

Telerehabilitation in the Home versus Therapy In-Clinic for Patients with Stroke

An assessor-blind, randomized, non-inferiority trial

Clinical Protocol

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TRIAL SYNOPSIS

Substantial evidence indicates that occupational and physical therapy improves outcomes after stroke, and that larger doses are associated with superior outcomes. However, many patients receive suboptimal doses of therapy for reasons that include cost, access, and difficulty with travel. This problem is likely to increase with time given the aging of the population and the increased rate with which patients survive stroke. Telehealth, defined as the delivery of health-related services and information via telecommunication technologies, has enormous potential to address this unmet need.

The current study will test the effectiveness of a novel home-based telehealth system designed to improve motor recovery and patient education after stroke. A minimum of 124 subjects (the number may be larger depending on the rate of subject dropout) with arm motor deficits 4-36 weeks after a stroke due to ischemia or to intracerebral hemorrhage will be randomized to receive 6 weeks of intensive arm motor therapy (a) in a traditional in-clinic setting or (b) via in-home telerehabilitation (rehabilitation services delivered to the subject's home via an internet-connected computer). The intensity, duration, and frequency of this therapy will be identical across the two groups, with subjects in both treatment arms receiving 36 sessions (18 supervised and 18 unsupervised), 80 minutes each (including a 10 minute break), over 6 weeks. The primary endpoint is within-subject change in the arm motor Fugl-Meyer (FM) score from the Baseline Visit to 30 Day Follow-Up Visit. Arm motor status is the focus here because it is commonly affected by stroke, is of central importance to many human functions, and is strongly linked to disability and well being after stroke.

Telerehabilitation will be evaluated using an assessor-blind, randomized, non-inferiority study design. This study seeks to establish comparable efficacy between the two treatment arms based upon a non-inferiority margin of 2.05 points on the arm motor Fugl-Meyer scale. Key study features include enrollment of a diverse stroke population, standardized and blinded outcomes assessment, a standardized treatment protocol, covariate-adaptive randomization, and use of an active comparator that is matched for duration, frequency, and intensity of therapy. The FDA has determined that this investigation is a non-significant risk device study.

A minimum of 5 clinical sites will participate in this study. Each clinical site will conduct all testing and treatment at a single central site, although each clinical site is encouraged to recruit subjects from their referral hospitals. At the central study site, an Assessment Therapist will perform all study testing, blinded to treatment assignment (the subject by necessity is not blinded), while a Treatment Therapist will provide in-clinic therapy as well as direct home-based telerehabilitation. Potential enrollees may be identified through any of several routes, for example, during the acute stroke admission at the clinical site or a referral hospital, during inpatient rehabilitation at the clinical site or a referral hospital, or through other means of community-based recruitment. Study conduct will be highly standardized, including selecting therapy content, delivering therapy, and testing.

The current study aims to critically evaluate the utility of a telehealth approach to motor therapy and stroke education. Telehealth has enormous potential to address unmet needs in the growing population of stroke survivors.

1. SPECIFIC AIMS/OBJECTIVES -

1.1. Specific Aim 1. Arm Motor Recovery:

Arm motor deficits are common after stroke, are strongly linked to disability and well being after stroke, and thus are the primary endpoint of this study. Aim 1 will test the hypothesis that subjects randomized to telerehabilitation will show significant arm motor gains, and that these gains will not be inferior to those achieved by subjects receiving intensive therapy in an outpatient clinic setting.

1.1.1 Primary Outcome: The primary endpoint is within-subject change in the arm motor Fugl-Meyer (FM) score from the Baseline Visit to the 30 Day Follow Up Visit.

1.1.2 Secondary Outcomes of Arm Motor Recovery: Two secondary endpoints will be examined, representing additional dimensions of motor recovery.

- (1) Within-subject change in Box & Blocks score from the Screening Visit to the 30 Day Follow Up Visit
- (2) Within-subject change in Stroke Impact Scale-Hand Domain score from the Baseline Visit to the 30 Day Follow Up Visit

1.2 Specific Aim 2. Secondary Outcomes--Stroke Education and Prevention:

Many patients with stroke know little about the causes of their condition and consequently have poor control of stroke-related risk factors. Improving patient knowledge about stroke can therefore help to prevent stroke recurrence and to optimize patient outcomes. While all certified stroke centers include patient education as a priority during the acute stroke admission, patients and their families may not be in the best position to benefit from such education at this time as compared to once they have returned to their home. Aim 2 will compare two different approaches to patient education in their impact on stroke knowledge, hypothesizing that both are effective, and are effective to an equal extent. As an extension of this issue, the degree of gains in stroke knowledge is hypothesized to be related to the extent to which patients implement appropriate lifestyle changes.

1.2.1 Subjects, having received targeted educational material for 6 weeks, will significantly increase knowledge related to stroke prevention and stroke risk factor control, measured as the change in percentage of questions answered correctly on the Stroke Education Exam from Screening Visit to Post-Therapy Visit.

1.2.2 The change in percentage of questions answered correctly on the Stroke Education Exam from Screening Visit to Post-Therapy Visit among subjects using the telerehabilitation system will be comparable to the change in percentage of questions answered correctly on the Stroke Education Exam among subjects using a traditional paper booklet-based method.

B.1.3 Increased stroke knowledge will be positively correlated with improvement in weight and blood pressure control.

1.3 Specific Aim 3. Patient Compliance with and Motivation for Therapy:

A major issue in rehabilitation therapy is patient compliance. Compliance and its variance across patients will be examined by measuring two dimensions of motivation. Aim 3 hypothesizes that compliance and activity-inherent motivation will be comparable across the two study treatment groups, and that compliance will vary with consequence-related motivation.

1.3.1 Compliance with therapy, defined as the percentage of the 36 therapy sessions for which the subject completed assigned activities for at least 40 minutes, will be comparable or better with telerehabilitation as compared to compliance with in-clinic therapy.

1.3.2 Activity-inherent motivation, which reflects how much a patient enjoys a therapy and defined as the change in score on the Physical Activity Enjoyment (PACES) Scale

from the Baseline Visit to end of the first week of therapy, will be at least as high (and in many patients higher) with telerehabilitation as compared to in-clinic therapy.

1.33 Level of consequence-related motivation, which reflects the patient's degree of dedication to treatment goals and defined as the score on the Optimization in Primary and Secondary Control (OPS) Scale at the Baseline Visit, will emerge as a significant predictor of compliance in both groups, even after controlling for key variables. When consequence-related motivation is high, compliance will be high, for both treatment groups. When consequence-related motivation is low, compliance may be lower but will vary with the level of activity-inherent motivation.

2. BACKGROUND AND SIGNIFICANCE

2.1 Rational and Supporting Data:

The burden of stroke disability is high and increasing.

There are >795,000 new strokes in the US each year. Most (>90%) patients survive the acute episode, living an average of 6-7 additional years¹. There are >7,000,000 adult stroke survivors in the U.S.². As a result, stroke is among the leading causes of human disability³ and the leading neurological cause of lost disability-adjusted life years⁴. This issue is increasing in magnitude: advances in stroke medicine are producing a sharp increase in the fraction of patients surviving the acute stroke, and so the burden of stroke disability will likely increase over time⁵. Consistent with this, Edwards et al found that significantly more individuals with stroke reported less dexterity and cognitive impairment in 2005 compared with respondents in 1996⁶. Several billion dollars are spent each year in the U.S. for stroke rehabilitation in an effort to improve patient outcomes. However, resources are contracting, for example, length of stay for inpatient rehabilitation is decreasing with time⁷, and quality of life after stroke is not improving over time⁶.

The most common deficits after stroke are in the motor system, present in >80% of patients initially. Between 55% and 75% of patients have enduring motor deficits, which are associated with reduced quality of life⁸⁻¹⁰. Arm motor deficits are of particular importance: 65% of patients at 6 months are unable to incorporate the paretic hand effectively into daily activities¹¹. Subjective well being is decreased one year after stroke, and this is mainly attributed to arm motor impairments¹².

Rehabilitation and brain plasticity after stroke.

Rehabilitation therapy achieves its effects by amplifying brain plasticity during the weeks of spontaneous recovery after stroke, and by stimulating new brain plasticity for subjects in the chronic phase¹³. The extent to which rehabilitation therapy promotes brain plasticity after stroke is influenced by several factors. Effects are greatest when therapy is challenging, repeated many times, task-specific, motivating, interesting, and intensive¹⁴⁻¹⁷. Patient autonomy to choose the details of therapy is also important. This approach, and other best practices identified from previous research, has been used to guide the therapeutic approach employed in the current study.

Greater rehabilitation therapy improves outcomes.

A large body of literature converges on the finding that greater amount and duration of motor therapy improves function and outcome after stroke¹⁸⁻²¹. This remains true when additional therapy is delivered in the home¹⁸, a point supported by meta-analysis by the Outpatient Service Trialists²². Similarly, greater intensity of rehabilitation care improves behavioral recovery^{23, 24}. In particular, high intensity functional arm training exercises maximize outcomes²⁵. The exact dose that defines intensive therapy is not clear.

Limitations of current practice stroke rehabilitation.

Not all patients receive post-stroke motor therapy of high duration, frequency, and intensity. There are several possible explanations. For some patients this is due to financial constraints. Some critics have charged that emerging reductions in duration of rehabilitation is limiting patient gains^{26,18}. In other cases, patients (e.g., in rural areas) cannot get to a rehabilitation therapy provider because it is too far from their home, or because of regional shortages of rehabilitation care²⁷. Cost-effective methods are needed to provide more rehabilitation therapy at higher intensities to patients wherever they live.

Stroke patients lack key knowledge and this affects their outcomes.

Compounding these issues is the overall modest control of stroke risk factors among survivors of stroke. At a time when patients are trying to recover and maintain function, many fail to control stroke risk factors. Risk factor control can prevent further vascular injury, recurrent stroke, myocardial infarction and progression of peripheral vascular disease--conditions that can have a large bearing on outcome after stroke. For example, the NHANES III study found that in 1,252 U.S. survivors of MI or stroke, blood pressure was controlled in only 53%; blood sugar, in only 50%; and blood cholesterol, in only 46%²⁸. While these results may be due to multiple factors, a likely contributor is that patients with stroke have limited knowledge about their condition. For example, 39% of ER patients with possible stroke could not name 1 sign or symptom of stroke in one study²⁹, and 40% of patients with stroke could not identify even a single stroke risk factor³⁰. Limited financial resources, time, and distance limit participation in educational programs in patients with neurological disease³¹. Yet this issue is of particular importance after stroke, as 1 in 6 stroke survivors will have a recurrent stroke³², which often introduces further disability. Education that improves awareness of control of modifiable stroke risk factors can improve risk factor control in patients with stroke³³⁻³⁵. Attention to stroke education can maximize behavioral gains from a stroke telehealth system^{36, 37}. Education of patients with stroke helps improve function and risk factor control, and thereby promotes favorable outcomes, and so is also a key focus in the current study

Telerehabilitation may be able to overcome some of the current limitations.

Telerehabilitation has been defined as "the delivery of rehabilitation services via information and communication technologies." Clinically, this term encompasses a range of rehabilitation and habilitation services that include assessment, monitoring, prevention, intervention, supervision, education, consultation, and counseling...."³⁸. Increasing evidence supports the potential of a telerehabilitation approach for reducing neurological deficits³⁹⁻⁴⁵. A major component of this may be derived from the use of games to promote patient participation in health care⁴⁶⁻⁵⁰. Games can motivate patients to engage in enjoyable play behavior which involves therapeutically relevant movements^{51, 52}. In addition, advances have been made using remote methods to improve function after stroke^{40, 53-55}, including motor function specifically^{39, 41, 43}.

Motivation.

A major challenge facing long-term rehabilitation care is to maintain patient motivation and engagement with physiotherapy. For example, 60-76% of patients do not adhere to a home-based physiotherapy treatment plan⁵⁶⁻⁵⁸. Even the best rehabilitation system will achieve little reduction in disability if not used. Successful rehabilitation interventions after stroke are strongly associated with high patient motivation⁵⁹. We will examine compliance in relation to two forms of motivation⁶⁰:

1. Activity-inherent motivation, which reflects how much a patient likes or dislikes the activity itself, independent of his or her commitment to the treatment goals.
2. Consequence-related motivation, which reflects the patient's level of motivational commitment to treatment goals.

Concerns have been voiced with stroke telerehabilitation studies to date.

Recent reviews of telerehabilitation provide useful points for designing a study of stroke telerehabilitation. A 2011 systematic review of stroke telerehabilitation⁵⁵ criticized the quality of published studies. Of 9 studies identified, only 4 were randomized controlled trials. On the positive side: “Home-based telerehabilitation interventions showed promising results in improving the health of stroke patients...Health professionals and participants reported high levels of satisfaction and acceptance of telerehabilitation interventions⁵⁵.” Despite this, the quality of the evidence was deemed “low”. In particular, sample sizes have been small, a control group was often not included, duration of follow-up was often brief, and most enrollees had mild deficits^{10, 55, 61, 62}--the latter being a perennial problem for stroke research⁶³. Few randomized controlled trials in stroke rehabilitation have considered compliance among their outcome measures³².

Guidance for stroke telerehabilitation design.

In addition to the above lessons, guidance for design of telerehabilitation comes from the 2008 Agency for Healthcare Research & Quality (AHRQ) report “Barriers and Drivers of Health Information Technology Use for the Elderly, Chronically Ill, and Underserved, which emphasized the importance of patient convenience, ease of use, frequent interactions with a clinician, and provision of feedback⁶⁴; the value of feedback in stroke rehabilitation has also been emphasized by other authors⁶⁵. These points guided the design of the trial's telerehabilitation system, and might explain the high compliance (97.9%) and low dropout (0%) in the pilot study (see Section III.C.). A 2012 report from the Institute of Medicine on telemedicine noted that “Some applications of telemedicine show great progress, but other areas lack large studies.” This report lauded the use of “matched control groups” and incorporation of “best practices into teletherapy content.”⁶⁶. Arsand et al⁶⁷ noted that many telehealth applications have not been “evaluated for their effectiveness in motivating or changing users’ self-management behaviors.” Motivation is key to changing patient habits, patterns, and outcomes, and is the centerpiece of Specific Aim 3. An overview of stroke rehabilitation from the American Heart Association noted that “interventions in which a variety of arm and hand movements are practiced have resulted in increased motor control and/or use of the paretic upper extremity in daily life tasks.”³². Each of these points informs the current study.

Telerehabilitation and context-specific training.

A potential advantage of telerehabilitation is that care is provided in a favorable context, and this might promote self-management. A core principle noted in occupational therapy practice guidelines is that performance after stroke is significantly influenced by the context of participation⁶⁸. Telerehabilitation provides therapy in the patient’s home and so builds on this principle^{59, 69, 70}. Furthermore, this approach can promote self-managed care⁶⁹ and thereby reduce costs⁶⁷; note too that a study from co-investigator Heckhausen et al in patients with recent stroke or myocardial infarct found that patients engaged in their own improvement had a major survival advantage⁷¹. These points are supported by a meta-analysis of day hospital vs. in-home care, which, while noting the limited amount of available data, found day hospital care to be no more effective and possibly more expensive. The authors called for further randomized trials that “focus on comparing services which aim to provide an equivalent intervention.”⁷²

3. PRELIMINARY STUDIES

A pilot study was completed at UC Irvine 12 subjects with chronic stroke, using entry criteria similar to the current proposal, each of whom received 28 days of home telerehabilitation targeting arm motor deficits. At baseline, age was 54±16 (mean±SD; range 26-75) yr, gender

6M/6F, time post-stroke 7 ± 6 mo, and arm motor Fugl- Meyer (FM) score was 39 ± 12 (range 23-56). The main results were that:

- **Compliance was excellent**
 - Subjects engaged in therapy 329 of 336 (97.9%) assigned days without dropout.
 - Verizon wireless USB modem reception was present in all patient's homes.
 - Subjects rated the experience very favorably via Likert scales.
- **Arm motor status was significantly improved**
 - Total FM score increased by 4.8 ± 3.8 points ($p=0.0015$).
 - Significant increases found in both proximal and distal FM subscores.
- **Gains in knowledge about stroke prevention were significant and specific to the practiced materials**
 - For questions practiced daily, scores increased 39% (22.8 to 31.7 out of 40, $p=0.0007$).
- **Findings were not dependent on computer skills**
 - Computer literacy scores, measured with the Computer–Email–Web Fluency Scale⁷³, declined with age ($r = -0.90$ to -0.92 , $p < 0.0001$), as expected, but were not related to gains in arm motor control or stroke knowledge.
- **Validated remote screening for depression after stroke**
 - Telehealth scoring of PHQ-9 ($r=0.72$, $p=0.008$) and PHQ-2 ($r=0.94$, $p < 0.0001$) were validated.
- **Subjects have poor recall of their recent usage and performance statistics**
 - Subjects were regularly asked to recall their scores and usage from the prior day, and whether these had changed. Their recall was not significantly related to actual values.

This pilot study suggests that home-based telerehabilitation is feasible in patients with recent stroke, indeed here being associated with 97.9% compliance. This approach significantly improved arm motor status, with average gains exceeding the minimal clinically important difference of 4.25 points⁷⁴. The same system was associated with significant increases in stroke prevention knowledge. These gains do not require computer literacy skills-- the laptop was changed from a computer into an appliance, as easy to use as a TV. Depression screening with this system was found to be valid and sensitive. Overall, conclusions were that a home-based telehealth system can be used to monitor, assess, and treat patients with the medically complex and heterogeneous condition that is stroke.

4. INVESTIGATOR EXPERIENCE

Dr. Cramer is a Professor of Neurology and Anatomy & Neurobiology at UC Irvine. He is also interim Director of the UC Irvine Stroke & Cerebrovascular Center, the Vice Chair for Research in the Dept. Neurology, the Clinical Director of the Stem Cell Research Center, and the Associate Director of the UC Irvine CTSA (Institute for Clinical & Translational Science). He is board certified in Neurology and in Vascular Neurology. His research focuses on brain repair after central nervous system injury in humans, with an emphasis on recovery of movement after stroke. Dr. Cramer has extensive experience running trials of restorative therapies in patients with stroke, including investigations of ropinirole⁷⁵, the growth factors beta-hCG and erythropoietin^{76, 77}, epidural brain stimulation⁷⁸⁻⁸⁰, repetitive transcranial magnetic stimulation⁸¹, exercise⁸²⁻⁸⁴, mental imagery⁸⁴⁻⁸⁶, robotics^{15, 87-93}, and a monoclonal antibody⁹⁴. Important to the current aims, Dr. Cramer also has a solid record of leadership experience in a clinical trial setting, with prior duties including DSMB member⁹⁵, IND author^{75, 76}, IDE coauthor⁸¹, co-PI⁹⁶ and

PI of international clinical trials^{77, 94, 97}. He was on the Advisory Board for the Centre for Stroke Recovery of the Heart and Stroke Foundation of Ontario for 10 years, and was co-Chair of the NIH Blueprint meeting: “Harnessing Neuroplasticity for Human Applications¹³.” He is past Chair of the Rehabilitation and Recovery Committee of the American Heart Association. Another leadership effort of note is starting the Orange County Stroke Society (Orange County, CA is the fifth most populous county in the US), leading a grassroots effort through this Society to create a new countywide system for acute stroke care delivery, getting this effort passed into law by the Orange County Board of Supervisors (on 5/7/09), then reporting the first year experience of this system (acute reperfusion therapy was administered at 5x the national average)⁹⁸. Dr. Cramer co-edited the book “Brain Repair after Stroke” (Cambridge University Press), is Assistant Editor at the journal *Stroke*, and is the author of over 200 manuscripts. Dr. Cramer will be in charge of running the overall study, maintaining interactions between team members, overseeing the contributions of each collaborator, maintaining all regulatory approvals, and submitting manuscripts to report final study results.

5. EXPERIMENTAL DESIGN AND METHODS

5. 1. Methods and Procedures

The current study will test the effectiveness of a novel home-based telehealth system designed to improve motor recovery and patient education after stroke. A total of 124 subjects with arm motor deficits 4-36 weeks after a stroke due to ischemia or to intracerebral hemorrhage will be randomized to receive 6 weeks of intensive arm motor therapy (a) in a traditional in-clinic setting –Standard therapy arm or (b) via in-home telerehabilitation (rehabilitation services delivered to the subject’s home via an internet-connected computer) - Investigational arm. The intensity, duration, and frequency of this therapy will be identical across the two groups, with subjects in both treatment arms receiving 36 sessions (18 supervised and 18 unsupervised), 80 minutes each (including a 10 minute break), over 6 weeks. Arm motor status is the focus here because it is commonly affected by stroke, is of central importance to many human functions, and is strongly linked to disability and well being after stroke.

5.2. Randomization

A web-based central randomization system developed by StrokeNet National Data Management Center (NDMC) and installed on the WebDCU™ Telerehabilitation Study website. Subjects will be assigned to one of the treatment groups according to the randomization scheme developed at the NDMC. Randomization will be done centrally using the WebDCU™ for all subjects entered in the trial. Covariate-adaptive randomization will be used to insure that values for (1) number of days post-stroke at time of randomization (2) FM score at the baseline visit, and (3) site are balanced across the two treatment groups.

5.3. Data Collection Schedule

Case Report Form	Screening	Baseline	End of 3 Supervised Sessions	End of 6 Supervised Sessions	End of 9 Supervised Sessions	End of 12 Supervised Sessions	End of 15 Supervised Sessions	End of 18 Supervised Sessions	Post-therapy	30 Day Follow Up	End of Study
Obtain Informed Consent	X										
Eligibility criteria	X										
Medical History	X										
Arm Motor Fugl-Meyer Scale	X	X							X	X	
Box & Blocks Test	X								X	X	
Montreal Cognitive Assessment	X										
Geriatric Depression Scale	X										
modified Ashworth Spasticity Scale(wrist)	X										
Nottingham Sensory Scale	X										
Blood Pressure & Weight	X									X	
modified Rankin Scale	X									X	
NIH Stroke Scale	X										
Stroke Knowledge Exam	X								X		
Non-study rehabilitation therapy	X	X	X	X	X	X	X	X	X	X	
(Pre-Stroke) Handedness Inventory		X									
Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X	X	
Stroke Impact Scale-Hand Subsection		X							X	X	
Physical Activity Enjoyment Scale (PACES)		X	X					X			
Optimization in Primary and Secondary Control Scale (OPS)		X	X					X			
Randomization		X									
Patient Satisfaction Questionnaire			X					X			
Adverse Events			X	X	X	X	X	X	X	X	
Therapy Compliance			X	X	X	X	X	X			
End-of-Study Form											X

Timing of Visits:

- Screening Visit: 3-35 weeks after stroke onset
- Baseline Visit: 1-21 days after Screening Visit (target value = 7 days), and 4-36 weeks after stroke onset

- First therapy session: 1-10 days post-randomization (target value < 5 days)
- Post-therapy Visit: 1-6 days after the last therapy session (target value = 2 days)
- 30 Day Follow Up Visit: 25-35 days after the last therapy session (target value = 30 days)

5.3.1 Screening Visit

The Screening Visit occurs 3 weeks to 35 weeks after the date of stroke onset. The study site will call the subject 1-2 days before the Screening Visit, reminding the patient of the time and place of the visit. Prior to signing informed consent, the subject will be given the opportunity to become familiar with the Box & Blocks⁹⁹ kit, and will be given the option to test him/herself given that only those persons who can score at least 3 blocks in one minute will be potentially eligible.

All procedures at the Screening Visit will be performed by one of the site's certified Assessment Therapists; in selected cases and with prior approval from the overall study PI (Dr. Cramer), a site may request to have a different member of the research team be trained, certified and approved for performing selected assessments. For a given patient, all assessments should be performed by the same Assessment Therapist, as reasonably possible, across the Screening, Baseline, Post-Therapy, and Day 30 Follow Up Visits.

The study will be explained to the subject, after which the subject will be asked to sign informed consent. Next, screening for eligibility will ensue, including medical history, Fugl-Meyer test^{100, 101}, Visual Acuity, Box & Blocks test⁹⁹, Montreal Cognitive Assessment¹⁰², the 3 rehabilitation exercise test examples (used to insure that the subject is able to successfully follow instructions), and the Geriatric Depression Scale (GDS)¹⁰³. Other measurements at this visit will include the modified Ashworth Spasticity Scale¹⁰⁴ of the wrist, the Nottingham Sensory Scale¹⁰⁵, blood pressure, weight, the modified Rankin Scale¹⁰⁶, the NIH Stroke Scale¹⁰⁷, and the Stroke Knowledge Exam. The amount of any therapy (OT, PT, SLT) that the subject received since the time of stroke onset and prior and concomitant medications will be documented. Note that the Screening Visit assessments, with the exception of the Fugl-Meyer test, may be completed thereafter up to and including at the Baseline Visit. This is not encouraged but it is recognized that this may be useful for selected patients.

Subjects deemed eligible at the end of Screening Visit will be given the time and date of the Baseline Visit.

Subjects who are found not to be eligible at this visit will be invited to return to be re-screened, e.g., in 1 month, provided the window for eligibility will still be open and providing that the basis for non-eligibility is potentially resolvable.

5.3.2 Baseline Visit

The Baseline Visit occurs 1-21 days after the screening visit (target value = 7 days), and 4-36 weeks after stroke onset. The study site will call the subject 1-2 days before this visit, reminding him/her of the time and place of the visit. The initial portion of this visit is performed by the Assessment Therapist. The Fugl-Meyer test^{100, 101} will be rescored, after which subjects will be scored on the Handedness Inventory¹¹⁰, and the Stroke Impact Scale-Hand Domain¹¹¹. The amount of any therapy (OT, PT, SLT) that the subject received since the Screening Visit and any new medications will be documented. Each subject will be asked to sign a behavioral contract^{113, 114}.

After final eligibility is determined, the remainder of this visit will be performed by one of the site's certified Treatment Therapist. Subjects will be randomized via WebDCUTM to 6 weeks of (a) in-clinic therapy or (b) home-based telerehabilitation in a 1:1 ratio. The Treatment Therapist will provide the subject with the PACES Scale^{108, 109} and OPS¹¹². The Treatment Therapist will then explain the details related to the subject's newly assigned rehabilitation therapy. For

subjects randomized to in-clinic therapy, this will include review of the content and design of therapy as well as details regarding the location where therapy will be delivered. For subjects randomized to telerehabilitation, the Treatment Therapist will review of the content of therapy and provide training on use of the telerehabilitation system.

The Treatment Therapist and the subject will then schedule the six weeks of therapy sessions.

Note that the Baseline Visit may be broken up into two separate visits not more than 3 days apart at the judgment of the research team. This is not encouraged but it is recognized that this may be useful for selected patients. If this Visit is broken into two separate visits, this will not change the fact that the first therapy session must be 1-10 days post-randomization.

5.3.3 Therapy Weeks 1- 6

For all subjects:

Across the two treatment groups in this study, intensity, duration, and frequency of intensive arm motor therapy will be carefully matched. The content of therapy will be standardized via use of specific study protocols, which are modeled after two main sources: *Upper-Extremity Task-Specific Training After Stroke or Disability* (Lang and Birkenmeier)¹¹⁴ and the *Accelerated Skill Acquisition Program* from the Interdisciplinary Comprehensive Arm Rehabilitation Evaluation study¹¹. In both treatment groups, therapy will include stretching, exercises, and functional training. Feedback, review of progress, and treatment plan revisions will be regularly shared with the study subject. All activities during the 6 weeks of therapy (treatment supervision, assessments, education) will be performed/overseen by one of the site's Treatment Therapist; the site's Assessment Therapists will not be involved with enrollees in any way during the 6 weeks of therapy. For a given patient, across the 6 weeks of study-related therapy, all treatment should be provided by the same Treatment Therapist, as reasonably possible.

Within 10 days of the Baseline Visit (target value < 5 days), all subjects will begin a 6-week regimen of study-designated intensive arm motor therapy (in-clinic vs. telerehabilitation). Prior to the first day of therapy, the Treatment Therapist will use the study manual of procedures to plan the specific content and details of therapy, incorporating subject data acquired at the Screening and Baseline Visits. The Treatment Therapist will revise this treatment plan twice thereafter (after 6 supervised sessions and again after 12 supervised sessions).

Therapy:

During each of the ensuing six weeks, all subjects will receive 6 therapy sessions/week, 3 of which will be supervised and 3 of which will be unsupervised. **Each subject will therefore receive a total of 36 therapy sessions**, consisting of **18 supervised therapy sessions** (Monday/Wednesday/Friday, when possible) **and 18 unsupervised therapy sessions** (Tuesday/Thursday/Saturday, when possible) as part of study participation. Each treatment session will be 80 minutes long, including a brief break. Interruptions in this schedule may be unavoidable in some cases, e.g., due to illness or during a holiday. When a supervised therapy session is missed, the study team will schedule a make-up supervised session for the subject. The goal is to have supervised sessions alternate with unsupervised sessions, but this is not required. Similarly, if a subject cannot perform an unsupervised therapy session on an assigned date, a make-up unsupervised session will be scheduled. The study will allow up to 8 weeks for completion of the 36 therapy sessions.

Subjects will be told that, if at any point during an unsupervised session a concern arises or a question comes up, they should wait until the next supervised session to ask the therapist if at all possible, but if the question is urgent they may call the study site. All such calls will be documented.

Assessments:

All subjects will undergo a brief set of assessments during the third supervised therapy session then again every 3 supervised sessions until the end of therapy. These assessments will record adverse events (which includes study-related adverse events, serious adverse events, and interval medical history), ascertain subject compliance with the unsupervised therapy sessions, document any new medications, and document the amount of any therapy (OT, PT, SLT) that the subject received outside of study procedures. At the end of supervised sessions 6 and 12, the subject will be briefly asked about any new interval medical history events. In addition, at the end of supervised session 3 and supervised session 18, the PACES, OPS scale, and Patient Satisfaction Questionnaire will each be completed. These brief assessments will be performed by the subject's Treatment Therapist.

Stroke education:

At the start of each of the 18 unsupervised sessions, all subjects will receive 5 minutes of stroke education. The information presented corresponds to the content of the Stroke Knowledge Exam, which focuses on prevention, recognition, response, and management of stroke. Subjects assigned to in-clinic therapy will review the stroke education booklet. Subject assigned to telerehabilitation will receive this information via the telerehab system.

5.3.3.1 Additional details for subjects randomized to in-clinic therapy:

The 18 supervised therapy sessions will take place at the central study site. A Treatment Therapist will provide continuous supervision throughout each of these 80 minute treatment sessions. A revised treatment plan will be generated and implemented after 6 supervised sessions and again after 12 supervised sessions of therapy.

The 18 unsupervised therapy sessions will take place in the patient's home, and will be guided by an individualized booklet generated and printed by the Treatment Therapist and distributed to the subject during the first in-clinic therapy visit. The content of the unsupervised therapy sessions will be matched to the same exercise and training components provided during the subject's in-clinic supervised therapy sessions. After 6 supervised sessions and again after 12 supervised sessions of therapy, the booklet guiding the unsupervised therapy session will be returned to the therapist, at which time a new booklet will be provided to the subject, containing a revised therapy plan. At the start of each of the 18 unsupervised sessions, all subjects will receive 5 minutes of stroke education. As with the other content of the unsupervised sessions, stroke education will be delivered by booklets provided by the Treatment Therapist during a supervised therapy session. Using a large Helvetica font, a multiple-choice question is presented, the patient marks his/her answer, then the patient is provided with the correct answer along with a brief explanation. This is repeated four times, for a total of five questions at each unsupervised session.

If there are any unsupervised therapy sessions completed after a subject's final supervised therapy session, the Treatment Therapist will call the patient at home and collect data on compliance for any such sessions.

5.3.3.2 Additional details for subjects randomized to telerehabilitation therapy:

A member of the study team will deliver the telerehabilitation system to the subject's home, set it up, confirm functionality, and review use of the system with the subject. Note that the telerehabilitation system will not operate for any process apart from telerehabilitation at any time, and will only provide telerehabilitation for the number of assigned minutes.

The 18 supervised therapy sessions will be performed by the subject, at home, using the telerehabilitation system. At the beginning of each supervised session, a Treatment Therapist at the central study site will initiate a videoconference with the subject's telerehabilitation system.

The Treatment Therapist will then supervise the subject, using a structured approach, for a 30 minute period during which the therapist will observe the patient performing assigned home-based telerehabilitation exercises and tasks, answer questions, review the treatment plan, and perform the brief study assessments during selected days. After 30 minutes, the therapist will disconnect from the videoconference, then the subject will complete the remaining 50 minutes of therapy, including a brief break, guided by the telerehabilitation system.

The 18 unsupervised therapy sessions will also be performed by the subject at home using the telerehabilitation system. There will be no contact with a study therapist during these sessions. Instead, all 80 minutes of therapy will be guided only by the telerehabilitation system. At the start of each of the 18 unsupervised sessions, subjects in the telerehabilitation group will receive 5 minutes of stroke education. As with the other content of the unsupervised sessions, stroke education will be delivered by the telerehabilitation system. A 5-level multiple-choice question is presented on the computer screen, the patient enters his/her answer, and then the patient is provided with the correct answer along with a brief explanation. This is repeated four times, for a total of five questions at each unsupervised session. All steps (read, answer, move forward, etc.) are timed, recapitulating the approach used successfully in our pilot study.

A revised treatment plan for the supervised and for the unsupervised therapy sessions will be generated and implemented after 6 supervised sessions and again after 12 supervised sessions of therapy, by the Treatment Therapist at the study site, then uploaded through the internet to the telerehabilitation system in the subject's home. Within 3 days of the last telerehabilitation therapy session, a member of the site study team will remove the telerehabilitation system from the subject's home.

5.3.4 Post-Therapy Visit

Immediately after the end of therapy (1-6 days following last day of therapy, target value = 2 days), the subject will return to the central study site for testing. The study site will call the subject the day before this visit, reminding him/her of the time and place of the visit. All testing during the Post-Therapy Visit will be performed by one of the site's Assessment Therapists, who will remain blinded to treatment assignment. To further protect the blinding of the Assessing Therapist, subjects will be reminded not to discuss with the Assessment Therapist any details of their six weeks of therapy. The assessments to be performed include FM Scale^{100, 101}, Box & Blocks Test⁹⁹, Stroke Knowledge Exam, and Stroke Impact Scale-Hand Subsection¹¹¹. Additionally, the Assessment Therapist will record adverse events (which includes study-related adverse events, serious adverse events, and interval medical history), document any new medications and will document the amount of any therapy (OT, PT, SLT) that the subject received outside of study procedures.

5.3.5 Day 30 Follow Up

Between 25 and 35 days after the last therapy session (target value = 30 days), the subject will return to the central study site for testing, including testing related to the primary study endpoint. The study site will call the subject 1-2 days before this visit, reminding him/her of the time and place of the visit. All testing during the Day 30 Follow Up Visit will be performed by one of the site's Assessment Therapists, who will remain blinded to treatment assignment. To further protect the blinding of the Assessing Therapist, subjects will be reminded not to discuss with the Assessment Therapist any details of their six weeks of therapy. The assessments to be performed include vital signs, FM Scale^{100, 101}, Box & Blocks Test⁹⁹, modified Rankin Scale¹⁰⁶, and Stroke Impact Scale-Hand Subsection¹¹¹. Additionally, the Assessment Therapist will record adverse events (which includes study-related adverse events, serious adverse events, and interval medical history), document any new medications and will document the amount of any therapy (OT, PT, SLT) that the subject received outside of study procedures

5. 4. Prohibited Therapy/Medication

Subjects may continue all therapy outside of study procedures as long as this non-study therapy does not interfere with the subject's fulfillment of study therapy and testing. The amount of any such outside therapy will be recorded at regular intervals.

The study protocol does not permit application of Botox to arm, leg, or trunk until after the 30 Day Follow Up visit is completed.

6. MANAGEMENT OF ADVERSE EVENTS

This study will collect adverse events deemed likely to have resulted from study procedures as well as serious adverse events (SAE). These will be submitted online through WebDCU™ and coded centrally using MedDRA¹¹⁵. The severity of any study-related adverse events and any SAEs will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE).

Adverse events will be reported per NIH StrokeNet Network SOP ADM12 Central Institutional Review Board (CIRB) Reporting. The Principal Investigator retains responsibility for reporting to the CIRB and the StrokeNet National Data Management Center (NDMC), which is housed in the Data Coordination Unit (DCU) in the Department of Public Health Sciences at the Medical University of South Carolina (MUSC) supports this reporting requirement. The Principal Investigator also remains responsible for all investigator duties stipulated under the NINDS Guidelines for Data and Safety Monitoring in Clinical Trials, last updated August 8, 2013. The Child Study Site Principal Investigators are responsible for reporting adverse events at their sites to the CIRB as detailed in SOP ADM12

7. CRITERIA FOR PREMATURE STUDY TERMINATION

Subject Removal from Therapy:

As participation in the "Telerehabilitation in the Home versus Therapy In-Clinic for Patients with Stroke" trial is voluntary, the subject may decline study therapy at any time. In addition, the treating investigator may stop study therapy if there is a safety concern. In either case, the subject will continue to be followed through the 30 Day Follow Up visit, unless informed consent is withdrawn.

Subject Withdrawal:

The subject has the right to voluntarily withdraw from the study at any time for any reason without prejudice to his/her future medical care by the physician or at the institution. For the occasional subject who withdraws consent, the date and reason for consent withdrawal should be documented. Subject data will be included in the analysis up to the date of the consent withdrawal. The distinction must be made between subjects who withdraw consent versus those who decline study therapy.

Procedure for Discontinuation:

The procedure to be followed at the time a subject withdraws consent from the trial:

- Check for the development of SAEs or study-related adverse events.
- Complete the End-of-Study form; include an explanation of why the subject is withdrawing consent.

Subject Lost to Follow-Up:

In the event that all possible attempts to locate the subject have failed, all efforts made by the investigator to contact the subject should be documented and the subject will be coded as lost to follow-up.

8. STATISTICAL CONSIDERATIONS, DATA ANALYSIS AND DATA MONITORING

In the study, populations used for testing comparable efficacy, the non-inferiority margin proposed for determining comparable efficacy, the statistical procedures used for summarizing and testing the primary and secondary comparable efficacy endpoints, and sample size justification for the proposed study. All analyses are two-tailed and use $\alpha=0.05$.

8.1 Analysis of populations:

Primary efficacy analyses will be conducted on the Intent-To-Treat (ITT) Population, defined as all subjects who are randomized. Sensitivity analyses for efficacy will also be conducted on the Per-Protocol Population, defined as all subjects who complete assigned activities for at least 40 minutes at 15 or more of the 18 supervised therapy sessions over a period of time extending no more than 8 weeks. In ITT analysis, for missing data such as due to subject lost to follow-up, multiple imputation using all available evaluation data will be utilized. No interim analysis is planned.

8.2 Summarization of safety data:

This is a low-risk interventional study, and the FDA has determined it to be a non-significant risk device study. As a result, no data and safety monitoring board is planned. Adverse events will be regularly assessed, and those considered likely attributable to study procedures will be documented, as will all SAEs. Within each treatment arm, the frequency and percentage of study-related adverse events and SAEs will be tabulated and reported by grade, system organ-class, and preferred term. Any study-related adverse events will be summarized as those leading to a specific intervention, those leading to study discontinuation, and by severity. Any SAEs will be reported similarly.

8.3 Key covariates:

Key covariates to include in the data analysis model are based on established predictors in this setting^{116, 117}: time post-stroke (number of days from stroke onset to randomization), severity of impairment (arm motor FM score at Baseline Visit), age, and enrollment site. Stroke subtype (ischemic vs. intracerebral hemorrhage) will also be included as a covariate.

Primary outcome measure:

The primary outcome measure is the within-subject change in arm motor FM score from Baseline Visit to 30 Day Follow Up Visit (Δ_{FM}). The higher the FM score, the better the outcome. Hence, with therapy, we anticipate the primary outcome measure will be an increase in FM score for each subject.

Non-inferiority margin:

The trial seeks to establish comparable efficacy based upon a non-inferiority margin of 2.05 (a value that is less than half the minimal clinically important difference for change in FM score) for the difference between the two treatment groups in the mean within-subject change in FM score from Baseline Visit to the 30 day Follow Up Visit. We consider a maximum of 30% smaller mean Δ_{FM} in the telerehabilitation group (as compared to the in-clinic treatment) to be clinically acceptable to consider it to be non-inferior. Based upon preliminary data, the mean Δ_{FM} for the telerehabilitation group is expected to be 4.80 points. Thus, if the assumed mean Δ_{FM} is 6.85 points in the in-clinic group, a reduction up to 30% (2.05 points) to 4.80 points in the telerehabilitation group would be concluded to be comparably efficacious.

Primary efficacy analysis:

The primary analysis of the Δ_{FM} will be conducted using an analysis of covariance (ANCOVA) model, adjusting for days from stroke onset to randomization, FM score at Baseline Visit, age, and enrollment site. The lower bound of the 95% confidence interval for the difference in Δ_{FM} between treatment groups will be used to assess comparable efficacy. If the lower bound of the 95% confidence interval for the difference in Δ_{FM} between groups (i.e., Δ_{FM}

for the telerehabilitation group - Δ_{FM} for the in-clinic group) is greater than -2.05, then we would declare telerehabilitation to be non-inferior.

Determination of sample size:

The objective of this study is to assess comparable efficacy of telerehabilitation vs. in-clinic intensive arm motor rehabilitation therapy with respect to the mean Δ_{FM} from the Baseline Visit to the 30 Day Follow Up Visit, using a non-inferiority margin of 2.05. Based on our pilot study, the mean Δ_{FM} in the telerehabilitation group is expected to be 4.80 with SD=3.80; extension to multiple sites and enrollment of subjects at earlier time points post-stroke may be associated with larger variance, and so a SD=4.0 is assumed. Comparable efficacy will be established provided that the lower bound of the 95% confidence interval for the difference in the Δ_{FM} between treatment groups is greater than -2.05. Assuming 80% power, the study will therefore seek to attain 30 Day Follow Up data on N=124 subjects (62 per arm). If the dropout rate is as high as 20%, then as many as 155 subjects may need to be enrolled.

8.4 Secondary efficacy analyses:

Two secondary endpoints examining change in motor status will be examined. Each examines treatment effects along an independent dimension, and will be analyzed as above. These are

- Within-subject change in Box & Blocks score from the Screening Visit to the 30 Day Follow Up Visit
- Within-subject change in Stroke Impact Scale-Hand Domain score from the Baseline Visit to the 30 Day Follow Up Visit

8.5 Secondary outcome measures:

Stroke education

- Gains in stroke knowledge from Screening Visit to Post-Therapy Visit, measured as the change in percentage of questions answered correctly on the Stroke Education Exam

In order to determine whether targeted educational material significantly increases subject knowledge related to stroke, the Stroke Knowledge Exam will be administered twice, once at the Screening Visit then again at the Post-Therapy Visit. A repeated measures ANOVA will be performed to determine if the percentage of Stroke Knowledge Exam answered correctly increases significantly from the Screening Visit to the Post Therapy Visit, controlling for days from stroke onset to randomization, initial Stroke Knowledge Exam score (at the Screening Visit), age, and enrollment site. To determine if gains in stroke knowledge vary according to the method by which stroke education is delivered, analysis will be repeated adding a time X group interaction term. Weight and blood pressure will be measured during the Screening Visit as well as during the Post Therapy Visit. In order to determine whether gains in stroke knowledge are associated with improvements in stroke risk factor control, the relationship between gains in stroke knowledge (the change in percentage of questions answered correctly on the Stroke Education Exam from the Screening Visit to the Post Therapy Visit) and improvement in weight and blood pressure control (change in weight, change in systolic blood pressure, and change in diastolic blood pressure) will be examined, controlling for days from stroke onset to randomization, Stroke Knowledge Exam score at Screening Visit, age, and enrollment site, and using a Bonferroni-adjusted alpha = 0.017; again, analyses will be repeated by adding a time X group interaction term.

Compliance and motivation.

- Compliance with therapy, defined as the percentage of the 36 therapy sessions for which the subject completed assigned activities for at least 40 minutes

Compliance with rehabilitation therapy will be examined across all 36 sessions. For supervised sessions, a subject will be considered compliant if at least 40 min of assigned

therapy has been completed, determined from the therapist notes for subjects in the in-clinic group and from telerehabilitation system usage data for subjects in the telerehabilitation group. For unsupervised sessions, a subject will be considered compliant if at least 40 min of assigned therapy has been completed based on self-report for the in-clinic group and by telerehabilitation system usage data for subjects in the telerehabilitation group. To determine whether compliance with therapy differs according to treatment group, ANCOVA modeling will be used to examine compliance across the 36 sessions as a function of treatment group, controlling for days from stroke onset to randomization, age, and enrollment site. Secondary analysis will examine compliance with only the supervised therapy sessions, as well as compliance with only the unsupervised sessions.

Motivation (assessed along two independent dimensions):

- Activity-inherent motivation, defined as the change in score on the Physical Activity Enjoyment (PACES) Scale from baseline to end of the first week of therapy
- Consequence-related motivation, defined as the score on the Optimization in Primary and Secondary Control (OPS) Scale at the Baseline Visit

Activity-inherent motivation reflects how much a subject likes or dislikes an activity itself, independent of his or her commitment to the treatment goals. To measure this, the PACES Scale will be scored three times (at the Baseline Visit, after 3 supervised sessions, and after 18 supervised sessions). Activity-inherent motivation will be defined as the change in PACES score. Primary analysis will examine the change from baseline to end of week 1, while secondary analysis will examine change from baseline to end of week 6. To determine whether activity-inherent motivation is different for in-clinic vs. telerehabilitation therapy, ANCOVA modeling will examine differential change in PACES score between the two treatment groups, controlling for days from stroke onset to randomization, PACES score at the Baseline Visit, age, and enrollment site.

Consequence-related motivation reflects a subject's level of commitment to treatment goals. To measure this, the OPS Scale will be scored three times (at the Baseline Visit, after 3 supervised sessions, and after 18 supervised sessions). We hypothesize that across both treatment groups, the baseline level of consequence-related motivation (OPS score at the Baseline Visit) will predict compliance with rehabilitation therapy. Furthermore, we hypothesize that when consequence-related motivation is high compliance will be high for both treatment groups, however when consequence-related motivation is low compliance may be lower overall but will vary with the level of activity-inherent motivation. ANCOVA modeling will be used to determine if consequence-related motivation is a significant predictor of compliance with therapy (as defined above, across all 36 sessions), controlling for days from stroke onset to randomization, age, and enrollment site. Primary analysis will define consequence-related motivation using the OPS subscale that measures selective primary and selective secondary control striving (also referred to as goal engagement). Secondary analyses will define consequence-related motivation using the entire OPS score, and will also examine the effect of treatment group. An additional analysis will examine add the interaction term OPS x PACES to determine whether compliance varies with consequence-related motivation in a manner that depends on level of activity-inherent motivation; PACES and OPS scores will be centered and then combined in the interaction term.

9. DATA COLLECTION, SITE MONITORING, DATA STORAGE AND CONFIDENTIALITY

Data management will be handled by the StrokeNet National Data Management Center (NDMC), which is housed in the Data Coordination Unit (DCU) in the Department of Public Health Sciences at the Medical University of South Carolina (MUSC). The study data will be

managed (including data queries) by the NDMC using the WebDCU™ system. This user-friendly web-based database system will be used for regulatory document management, subject randomization, data entry, data validation, project progress monitoring, subject tracking, user customizable report generation and secure data transfer. The study database only identifies study subjects by unique study identification codes. All data will be stored in a manner that is HIPAA compliant, without the ability to track the information back to a specific subject except through a password protected system. All collected information about a subject will be stored by a unique identification code. All NDMC personnel are certified by the NIH Office of Human Subjects Research in the Protection of Human Research Subjects.

UC Irvine personnel will perform site monitoring. At site initiation, topics covered will include responsibilities of each study team member, review of study procedures and case report forms, confirmation that needed resources are available to the study team, and designation of separate spaces for assessment and therapy. Monitors will visit each site approximately every 4 months thereafter. The monitor will review signed consent forms, perform source document verification on a subset of the data collected, and review study procedures with the site team. In selected cases, site initiation and site monitoring visits may be conducted using teleconference methods.

10. SETTING

A minimum of 5 clinical sites will participate in this study. Each clinical site will conduct all testing and treatment at a single central site, although each clinical site is encouraged to recruit from their referral hospitals. Potential subjects may be identified through any of several routes, for example, during the acute stroke admission at the performance site or a referral hospital, during inpatient rehabilitation at the performance site or a referral hospital, or through other means of community-based recruitment. Towards this, when a patient admitted for acute stroke or for inpatient rehabilitation is considered potentially eligible for the study, the medical record may be reviewed by virtue of the partial HIPAA waiver obtained as part of this study. This review of the medical record might include clinical, laboratory, and radiological data in order to help the study team better determine whether this patient is potentially eligible for this study or not. At each clinical site, the designated location where Assessment Therapists perform their testing must be spatially separated (a different building or floor) from the designated location where Treatment Therapists interact with subjects. This is critical to insuring that the Assessment Therapists remain blinded to treatment assignment.

11. KEY PERSONNEL AND FACILITIES

At the clinical site, an Assessment Therapist will perform study testing of primary and secondary efficacy analyses, blinded to treatment assignment (the subject by necessity is not blinded), while a Treatment Therapist will oversee therapy to subjects in the in-clinic and the telerehabilitation groups. Study conduct will be highly standardized, including selecting therapy content, delivering therapy, and testing.

11.1 Study team members at each clinical site

Site lead investigator:

The lead investigator at each site will be responsible for supervising and coordinating study procedures, including monitoring study progress and enrollment, as well as insuring that study conduct conforms to all study policies. Although study-related adverse events and SAEs are deemed highly unlikely, reporting and responding to any such reports will be the responsibility of the lead investigator.

Two or more Treatment Therapists (licensed occupational therapists or licensed physical therapists, none of which is also an Assessment Therapist):

The Treatment Therapist will oversee and provide study-related therapy. The intent is to have one therapist at each site provide therapy for all enrollees across both treatment groups, with an additional therapist available as backup; if this is not possible, a secondary priority is that a patient receives all of his/her therapy from a single study Treatment Therapist. The Treatment Therapist will also oversee subject randomization, which occurs after completion of all eligibility and baseline testing, as well as those tests that are scored during the six weeks of therapy.

Two or more Assessment Therapists (licensed occupational therapist or licensed physical therapist, none of which is also a Treatment Therapist):

One of these assessment therapists is designated as the primary Assessment Therapist and the other as backup. The intent is to have all study assessments performed by a single Assessment Therapist across all enrollees over time at each site; if this is not possible, a secondary priority is that a patient receives all of his/her assessment from a single study Assessment Therapist. Study procedures are designed to ensure that the Assessment Therapists remain blind to subject treatment assignment. The Assessment Therapist will also oversee informed consent as well as verification that all entry/exclusion criteria are satisfied.

A study coordinator:

The study coordinator will assist with phone calls, correspondence, recruitment procedures, site monitoring visits, scheduling enrollee appointments, telerehabilitation system delivery to and removal from the subject's home, regulatory document submission, and data entry. The study coordinator will also oversee intake, checkout, inventory, functionality checks, and updates for the telerehabilitation system components.

11.2 Site training, certification, and monitoring

A one-day investigator meeting will be organized at UC Irvine prior to first patient enrollment, with key personnel from each site in attendance. This meeting will provide training on all study policies and procedures, including standardized in-clinic therapy, standardized use of the telerehabilitation system, and all subject assessments. Prior to attending this training meeting, all Treatment Therapists and Assessment Therapists will be required to successfully complete respective online study training modules; for the Assessment Therapists, this will include online certification on the NIH Stroke Scale, the modified Rankin Scale, and the FM scale. Assessment Therapists will also be required to successfully undergo formal online recertification on the FM scale every 4 months following this meeting. A grace period may be granted per PI discretion.

11.3 Hardware provided to each clinical site

Each clinical site will receive 2-3 telerehabilitation systems, 4 exercise kits for home use, 1 assessment kit and 1 set of treatment materials for in-clinic use for patients randomized to in-clinic rehabilitation therapy. These will be shipped from UC Irvine. At the conclusion of the study, all equipment provided must be returned to UC Irvine. In order to minimize inter-site differences in content of therapy, sites are to limit therapy-related devices to those provided, for both the telerehabilitation and the in-clinic therapy groups.

Components of the telerehabilitation system:

- Table (folding legs, 36"W x 36"D)
- Folding chair (no arms, extra large padded seat)
- Power extension cord with surge protector
- Computer including monitor, microphone, speakers, bluetooth, and power cord
- USB Hub including cable and power cord

- Verizon wireless modem
- Tabletop multi-device organizer
- Myo Band
- Wiimote, pistol holder, IR emitter
- PowerMate USB (2)
- PlayStation 3 Eye Move Controller
- Joystick
- Logitech Trackpad
- Verve hub, sensors, and buttons
- Standard rehabilitation therapy devices for the upper extremity

12. ESTIMATED PERIOD OF TIME TO COMPLETE THE STUDY

The target enrollment rate is at least 2 patients enrolled per month per site. Enrollment of 124 subjects with complete data is planned; assuming a dropout rate as high as 20%, as many as 155 subjects may need to be enrolled. Assuming 8 clinical sites participate, each site will enroll approximately 20 subjects, which may require 10 months. Permitting 2 months for sites to ramp up enrollment, allowing 1 month reduced activity during the winter holidays, and recognizing that the study will run for 3 months after enrolling the final subject (from Screening Visit to 30 Day Follow Up Visit), the study is expected to run approximately 16 months from enrollment of the first patient to completion of the last patient. Data cleaning (including final monitoring visits) and statistical analysis is expected to take up to an additional 6 months.

13. HUMAN SUBJECTS

13.1 Sample Size:

A total of 124 subjects completing all treatment and testing is desired; assuming a dropout rate as high as 20%, as many as 155 subjects may need to be enrolled. Patient characteristics, including number, age range, and health status, will in all cases conform to the below Inclusion/exclusion criteria. There are no special classes of subjects.

13.2. Inclusion/Exclusion Criteria:

Inclusion criteria

1. Age \geq 18 years at the time of randomization
2. Stroke that is radiologically verified, due to ischemia or to intracerebral hemorrhage, and with time of stroke onset 4-36 weeks prior to randomization
3. Arm motor FM score of 22-56 (out of 66) at both the Screening Visit and Baseline Visit
4. Box & Block Test score with affected arm is at least 3 blocks in 60 seconds at the Screening Visit
5. Informed consent signed by the subject
6. Behavioral contract signed by the subject

Exclusion criteria

1. A major, active, coexistent neurological or psychiatric disease, including alcoholism or dementia
2. A diagnosis (apart from the index stroke) that substantially affects paretic arm function
3. A major medical disorder that substantially reduces the likelihood that a

- subject will be able to comply with all study procedures
4. Severe depression, defined as GDS Score >10
 5. Significant cognitive impairment, defined as Montreal Cognitive Assessment score < 22
 6. Deficits in communication that interfere with reasonable study participation
 7. A new symptomatic stroke has occurred since the index stroke that occurred 4-36 weeks prior to randomization
 8. Lacking visual acuity, with or without corrective lens, of 20/40 or better in at least one eye
 9. Life expectancy < 6 months
 10. Pregnant
 11. Receipt of Botox to arms, legs, or trunk in the preceding 6 months, or expectation that Botox will be administered to the arm, leg, or trunk prior to completion of the 30 Day Follow Up Visit
 12. Unable to successfully perform all 3 of the rehabilitation exercise test examples
 13. Unable or unwilling to perform study procedures/therapy, or expectation of non-compliance with study procedures/therapy
 14. Concurrent enrollment in another investigational study
 15. Non-English speaking, such that subject does not speak sufficient English to comply with study procedures
 16. Expectation that subject cannot participate in study visits
 17. Expectation that subject will not have a single domicile address during the 6 weeks of therapy, within 25 miles of the central study site and with Verizon wireless reception.**

**A site may enroll a person who does not meet exclusion criterion # 17 if this is specifically approved by the site's study PI.

**Because Montreal Cognitive Assessment scores may be difficult to interpret for patients with aphasia, at the discretion of the site's study PI, exclusion criterion #5 ("MoCA score cannot be <22") can be waived.

13.3 Intended gender, the age range, intended racial and ethnic distribution, and if vulnerable subjects:

The recruitment process will not involve any restrictions on socio-demographic factors including gender or ethnic characteristics of the patient population. Children age 18-21 will be permitted study enrollment; younger children will not be offered enrollment because stroke and stroke recovery are very different in younger brains and require separate study. The composition of the study population will depend on patient sources available to the enrolling sites.

All subjects must be able to sign their own consent and speak sufficient English to comply with study procedures.

13.4 Identifying the source of the study population:

Some potential enrollees will be identified when they contact an enrolling site in response to an advertisement or the study website. Others will be identified during the acute stroke admission at the clinical site or its referral hospitals, or during the stroke rehabilitation admission at the clinical site or its referral hospitals; as described in Section 10 (above), the medical record of patients considered potentially eligible for the study may be reviewed by the study team in order to help determine whether such a patient is potentially eligible for this study or not. Most patients contacted during the acute stroke admission or during the stroke rehabilitation admission will be at too early a stage post-stroke to be eligible for the study, and so these

subjects will be offered the opportunity to share their contact data with study personnel, so that study personnel can contact them at a later time, when they may become study eligible.

13.5. Plans for recruitment of subjects:

A study flyer will be generated and individualized for each site. The methods used for recruitment of subjects in the study will be devoid of any procedures that may be construed as coercive.

Beginning 3-4 weeks after stroke onset, potential enrollees will be contacted monthly until week 35 post-stroke, and asked if they remain potentially interested, and if so if they are ready to participate. Those who are ready to participate will be given a very brief phone screen related to eligibility. Those who are not interested will be removed from the list of potential enrollees. Those who are not ready but remain potentially interested will be informed that they will be contacted again in a month's time, unless it is 35 weeks post-stroke, in which case the patient will be informed that they will no longer be contacted as the window for eligibility is closing.

A phone screen for those who are interested in enrolling takes < 5 minutes and asks (1) date of their stroke onset, and if they (2) live <25 miles from the clinical site, (3) are \geq 18 years old, (4) speak sufficient English to participate, (5) can commit to 18 in-clinic sessions (given the 50% chance of being randomized to this group), and (6) can likely score at least 3 on the Box & Block Test (can grasp an inch-wide object with the paretic hand, lift it off the table 6 inches into the air, then set it back down onto the table, at least three times in one minute). If these 5 questions are all answered in the affirmative, he/she will be invited to the clinical site for the Screening Visit.

Informed consent Process:

Consent will be obtained by an approved investigator at the performance site during the Screening Visit. The consent must be the IRB-approved version corresponding to the version of the protocol approved when the subject was consented. Signed informed consent must be obtained from the patient before any procedure, done solely for the purposes of research, is conducted. Consent by a legally authorized representative and verbal consent are not allowed for this study. As in all trials, the goal is to achieve a high level of compliance with protocol requirements by assuring that the potential subject is fully informed and agrees to the protocol requirements. In addition, patients with a strong likelihood of non-adherence, as described in the eligibility criteria, should not knowingly be randomized. Careful assessment of the patient's understanding of the trial is required prior to enrollment.

Screen failure Logs:

Screen failure logs at each site will be entered into the study database listing all patients who sign consent and are then screened, but are not randomized into the Telerehabilitation Trial. Documentation will include demographic information and reasons for non-enrollment. No other data will be entered into WebDCU™ for screen failures. Screening data will be periodically reviewed by the UC Irvine team to insure that full efforts are being made with respect to recruitment and enrollment, and to identify any patterns with regard to ineligibility or reasons for non-enrollment.

14. RISK/BENEFIT ASSESSMENT

14.1. What is the level of risk?

The FDA has determined that this investigation is a non-significant risk device study.

14.2. How does the anticipated benefit justify the risk, and Is the anticipated benefit of this research at least as favorable to the subjects as available alternative approaches?

Usage of the telerehabilitation system might confer some direct reduction of post-stroke disability or post-stroke complications. An indirect benefit of participating in the study is to society via an improved understanding of the factors related to home-based telerehabilitation. Because of the research methods and screening approaches to be adopted, as described above, the risks to subjects are considered very small. The potential value of the information to be learned might be high. Therefore, the risk-benefit analysis for participation in the proposed studies is considered to be reasonable.

14.3. Does this research represent an increase over minimal risk?

No.

14.4. How does this research present experiences to subjects that are reasonably commensurate with those inherent in their actual or expected everyday life situations?

Post-acute stroke the use of intensive rehabilitation therapy is considered standard of care and is routinely prescribed either as inpatient or outpatient treatment. It is anticipated that the population enrolled in this trial will be experiencing or will have experienced some form of rehabilitative therapy that would provide a frame of reference for the subjects. The introduction of telerehabilitation technology may be novel to a subject but explanations will be provided during the consenting process.

14.5. How this research may yield generalizable knowledge?

Stroke is among the leading causes of adult disability. A number of factors highlight the potential for telehealth methods to improve patient outcomes, in an economical way. Bringing these issues to broad usage requires further study on many fronts. Some of these issues are addressed in this study.

14.6. Describe any potential RISKS OR DISCOMFORTS in detail.

Overall the risks related to this study are small. One potential risk related to study participation is breach of security for data handling, which could potentially result in a loss of privacy of sensitive medical/neurological information. A number of steps to safe guard Information will be taken including the use of locks for files and use of passwords for computer files to maintain this risk as extremely small. All computer signals from the subject's home to the lab will use methods that maximize security. The computer provided for home use will contain no personal information. Any data related to a subject's arm motor function is labeled with the subject ID number and has no identifying information.

A second potential source of potential risk is the telerehabilitation system. The risk of hardware is expected to be extremely small. The risk of daily participation for 6 weeks is also expected to be extremely small. Nonetheless, some of the methods to be pursued in the proposed study are untested and so could expose the patient to unexpected risks. We will remain sentinel for these by using close-ended and open-ended questions during live and during telecommunication call interviews with patients.

A third potential source of potential risk is the behavioral testing. This can produce fatigue, a possibility for which trial investigators and staffs will be trained to remain sentinel. Procedure training will reinforce the use of offering subjects breaks for rest, snacks and bathroom use routinely.

15. PAYMENT

After completion of the 6 weeks of therapy, the subject will be given \$50, to help with transportation and parking. If the subject leaves the study early for any reason, they will be provided with appropriate compensation to help with transportation and parking costs while in the study.

16. SUBJECT COSTS

There is no cost to the subject or the insurer/third party payer for participation in the study.

17. CONSENT FORM

A separate consent form template has been generated and is attached.

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APPENDICES: 1. Informed Consent Template (Amendment #1, Version 2)**Consent to Participate In a Research Study**

Study Title: “Telerehabilitation in the Home versus In-Clinic for Patients with Stroke. *An assessor-blind, randomized, non-inferiority trial*”

IRB Study #:

Sponsor Name: Steven C. Cramer, MD
NINDS/NIH

Investigator Information:

Steven C. Cramer, MD

Protocol Principal Investigator Name

{INSERT TEXT HERE}

Local Site Name

{INSERT TEXT HERE}

{INSERT TEXT HERE}

Local Principal Investigator Name
Contact

Telephone Number 24 hr Emergency

Subject Name: _____

Date of Birth: ____/____/____

INTRODUCTION:

A biomedical or health-related research study is performed to answer specific questions about a disease.

Before you agree to participate in this research study, it is important that you be told the purpose, procedures, benefits, risks, discomforts, and precautions of the research. You should also be told what alternative procedures are available to you if you do not participate in the research study. The informed consent document is a written summary of this information. Be sure to ask questions while you read this consent document and ask questions if there is anything that you do not understand.

Your participation in this research study is entirely voluntary.

You may choose either to take part or not to take part in this research study. If you decide to take part, you may decide to leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to you.

The researcher and sponsor of this study do not promise that you will receive any benefits from this study.

WHY IS THIS RESEARCH BEING DONE?

Occupational and physical rehabilitation therapy (OT and PT) may help a person recover after stroke. The amount of therapy a person receives may affect recovery. Larger doses of therapy may work better. Some patients may receive too small a dose of therapy. This may be related to high cost, limited access, and difficulty with travel.

Telehealth methods may help address this problem. Telehealth allows people in their homes to use the internet to obtain healthcare from medical professionals.

Telerehabilitation is a type of telehealth. It allows a patient to use the internet to obtain rehabilitation therapy at home.

The main purpose of this study is to find out if telerehabilitation is as good as therapy provided in person to help people recover from a stroke. Another purpose of the study is to find out if providing educational materials improves understanding of stroke prevention and risk factor control.

WHY HAVE YOU BEEN ASKED TO TAKE PART IN THIS RESEARCH STUDY?

You are being asked to take part in this research study because you are at least 18 years old, and you have been diagnosed with stroke that caused arm weakness.

HOW LONG WILL YOU BE IN THE RESEARCH STUDY?

You will be in the research study for approximately 10-12 weeks.

You will have six weeks of in-clinic therapy or home-based telerehabilitation therapy.

There will be 6 sessions of therapy per week. There will be 3 supervised sessions per week and 3 unsupervised sessions per week. You will have 18 supervised and 18 unsupervised sessions. You will have a total of 36 therapy sessions.

Each therapy session lasts 80 minutes, including a brief break.

You are free to withdraw from this study at any time. If you decide to withdraw from this study you should notify the research team immediately. The research team may also end your participation in this study if you do not follow instructions, miss scheduled visits, your safety and welfare are at risk, or if the study sponsor decides to stop the study.

If you experience any of the side effects listed in the Risks and Discomforts section or if you become ill during the research, you may need to be withdrawn from the study, even if you would like to continue. The research team will make the decision and let you know if it is not possible for you to continue. Such a decision may be made to protect your safety and welfare.

If you withdraw or are removed from the study, the reasons for study exit will be discussed with you and all questions will be answered. You will not be required to undergo any procedures to exit the study.

WHO IS CONDUCTING THE RESEARCH STUDY?

This study is sponsored by the National Institutes of Health. The study is directed by Dr. Steven C. Cramer, a researcher at the University of California, Irvine. Medical supervision for this study is provided by Dr. Cramer.

This study is conducted by {INSERT LOCAL SITE INVESTIGATOR's NAME} at {INSERT LOCAL SITE NAME}.

HOW MANY PEOPLE WILL TAKE PART IN THE RESEARCH STUDY?

A total of 8-12 different sites in the United States will enroll a total of 124 patients into this study.

WHAT IS INVOLVED IN THE RESEARCH STUDY?

You will be randomized to either the “in-clinic therapy” or “telerehabilitation therapy” group. Randomization means that you are put into a group completely by chance. It is like flipping a coin.

You and the treatment therapists that provide your therapy will know the group you are in. The study assessment therapist who examines you over time will not know the group into which you are randomized. Please do not share this information with the assessment therapist.

If you are randomized into the “in-clinic therapy” group you will,

- Go to the clinic 4 times for testing
- Go to the clinic 18 times for rehabilitation therapy
- Perform 18 days of rehabilitation in your home using an instructional booklet.

If you are randomized into the “telerehabilitation therapy” group, you will,

- Go to the clinic 4 times for testing

- Perform 36 days of telerehabilitation practice in your home, using a computer-based telehealth system.

Therapy will include arm stretching, exercises, and functional training. The treatment therapist will provide feedback, review your progress, and make any changes needed in the therapy plan.

Each therapy session lasts 80 minutes, including a brief break.

The treatment therapist will ask you about any problems you may have had with the therapy. The treatment therapist will also ask about the amount of any occupational, physical, speech, or other therapy you received outside of study procedures.

You will undergo some brief testing to monitor your progress.

There may be times when you need to miss a treatment session. If you miss a therapy session, a make-up session will be scheduled. You are allowed up to 8 weeks to complete study therapy.

You will have intensive arm therapy 6 days per week for 6 weeks in a row in this study.

You may receive rehabilitation therapy that is not part of this study as long as it does not interfere with you completing study testing and therapy. This non-study therapy may include occupational, physical, or speech therapy. You may not receive Botox treatments to your arm, leg, or trunk until after Visit 4 is completed. Botox (or botulinum toxin) is sometimes used to help a stiff muscle relax after a stroke. We will record the amount and type of non-study therapy you receive at each of the assessment visits.

Visit 1 All Participants:

This visit will occur 3 weeks to 35 weeks after your stroke. We will ask you to sign the current "informed consent" form, then determine whether you are eligible to be in this study. We will ask you questions about your medical history. You will also perform activities to test your strength, arm function, mood, and which hand you prefer to use. If you are eligible for this study, you will return for Visit 2.

Visit 2 All Participants:

This visit occurs 1-21 days after Visit 1. We will recheck the function in your stroke-affected arm. Note, if necessary this visit may be broken up into two separate visits not more than 3 days apart.

Behavioral contract: You will sign a behavioral contract. The contract will indicate that you and the therapist agree on your main goals and on what you will do as during the study. This is not a legal contract and is not binding in any way. It does ask you to commit to specific details such as when you will perform your therapy.

If you meet all entry criteria, you will be randomized to 6 weeks of either “in-clinic” therapy or home-based “telerehabilitation” therapy.

This therapy will begin within 10 days after Visit 2.

Subjects randomized to in-clinic therapy

You will have 18 sessions of supervised therapy, which take place at University of California Irvine, plus 18 sessions of unsupervised therapy, which take place in your home.

You will perform arm exercises and training during these visits. The study will guide your treatment therapist regarding choices and approaches for therapy. Each session will be 80 minutes long, including a brief break. It is important that you adhere strictly to the assigned number of minutes.

Your treatment therapist will give you your therapy plan at the end of visit 2.

Supervised in-clinic therapy: You will receive 3 supervised sessions per week (Monday/Wednesday/Friday when possible) for 6 weeks. There will be a total of 18 supervised sessions. The treatment therapist will supervise these visits.

Unsupervised home-based therapy: You will perform 3 unsupervised sessions per week (Tuesday/Thursday/Saturday when possible) for 6 weeks at your home. You will follow the

directions in the booklet given to you by your treatment therapist. You will return the booklet once you complete the assignments. You will also be provided with information related to prevention, recognition, response, and management of stroke.

If there are any unsupervised therapy sessions completed after the last supervised therapy session, the Treatment Therapist will call you at home and collect data regarding these sessions.

Subjects randomized to telerehabilitation therapy

We will deliver the telerehabilitation system to your home and set it up for you. This system consists of a laptop computer and a table on which the laptop is placed. The laptop also has several devices connected to it that you will use as part of your rehabilitation practice. The laptop will need to be plugged into an electrical socket in your home. We will make sure the system is working properly and show you how to use it. The laptop has a camera and a wireless communication card. We will use the card to talk to you, to see how your rehabilitation practice is going and to adjust your rehabilitation practice settings. The choices and approaches for therapy will vary across patients and will be guided by the study and by your therapist. After you complete the 6 weeks of therapy, we will make an appointment to come back to your house to remove the telerehabilitation system.

You should not use the home telerehabilitation system for more than 80 minutes a day. The system is programmed to limit daily use to 80 minutes. Nobody besides you should use your telerehabilitation system. At the start of each therapy session, the system will take some pictures of you as you perform certain tests to make sure of this. The computer and telerehabilitation system will not operate for anything other than the planned telerehabilitation.

You will be introduced to your telerehabilitation system at the end of Visit 2.

Home-based telerehabilitation therapy: The treatment therapist will plan the therapy before the first day of telerehabilitation. The treatment therapist will revise the plan every two weeks as needed.

You will have 18 sessions of supervised and 18 sessions of unsupervised therapy. The treatment therapist will arrange a videoconference with you through your telerehabilitation system for the supervised therapy sessions. All of these sessions take place in your home using

the telerehabilitation system. At each session, you will exercise for 80 minutes, including a brief break.

Home-based supervised therapy: You will receive 3 supervised sessions per week of intensive arm motor therapy, for 6 weeks. These sessions will be done on Monday, Wednesday, and Friday when possible. You will have a total of 18 supervised therapy sessions. An occupational or physical therapist located at the study site will use the videoconference feature of the telerehabilitation system to supervise first 30 minutes of each of these 18 sessions. You will also undergo some brief testing. The treatment therapist will ask you about any problems you may have had with the therapy. The treatment therapist will also ask about the amount of any occupational, physical, speech, or other therapy you received outside of study procedures.

Home-based unsupervised therapy: You will also be assigned 3 home-based unsupervised sessions per week for 6 weeks. These sessions should be done on Tuesday, Thursday, and Saturday when possible) You will do these sessions in parallel with the supervised sessions. You will use the telerehabilitation system to do the same exercises and training, but with without supervision. We will also provide you with information related to prevention, recognition, response, and management of stroke.

Visit 3 All participants

Within 6 days after the end of therapy, you will be asked to return to the study site for testing. The assessment therapist will ask you about any problems you may have had with the therapy. The assessment therapist will also ask about the amount of any occupational, physical, speech, or other therapy you received outside of study procedures.

Visit 4 All participants

One month after Visit 3, you will be asked to return to the study site for a final round of testing.

WHAT ARE THE RISKS AND DISCOMFORTS OF THE RESEARCH STUDY?

The possible risks and/or discomforts of this study are expected to be minimal. You may experience some fatigue and muscle soreness after moving your stroke-affected arm during rehabilitation practice. You should immediately inform the study team if this is severe.

Because some visits might be prolonged, for example possibly spanning more than two hours, study participation also carries the potential risk of general fatigue. We will always try to be sensitive to this possibility, and offer a break, a light snack, water or a bathroom break as needed. Of course, you can request any of these at any time.

As part of study participation, information about you will be collected then retained on paper and in computer files. Great care will be taken to safeguard all forms of such information, for example using locks for files with paperwork and using passwords for computer files. However, the possibility remains that a determined thief might try to steal information. Thus, one risk of study participation is that information about you could be stolen.

Since the study involves a laptop and video phone calls, it is possible to have a breach of confidentiality that would result in your private information being seen by others. We have gone to great lengths to prevent this. All computer signals from your home to the lab will use methods that maximize security. The same methods that doctors use to treat patients when remote computers are used will be used in this study. It is possible that the laptop could be stolen or used by someone who is either not you or not an investigator. However, the laptop will contain no personal information. Any data related to your arm motor function is labeled with only your study ID number and has no identifying information.

There may be unknown or unforeseen risks associated with study participation.

ARE THERE BENEFITS TO TAKING PART IN THE RESEARCH STUDY?

There may not be a direct medical benefit to you from taking part in this study. The information learned from this research study may benefit other patients with stroke in the future.

WHAT OTHER CHOICES FOR CARE ARE THERE?

The other choice for care is standard occupational therapy or physical therapy prescribed by your physician through the outpatient and inpatient rehabilitation clinics.

WHAT IS THE CLINICAL TRIALS REGISTRY?

A description of this clinical trial will be available on www.clinicaltrials.gov, as required by U.S. Law. ClinicalTrials.gov is a registry and results database of publicly and privately supported clinical studies of human participants conducted around the world.

This Web site will not include any information that can identify you. At most, the Web site will include a summary of the study design and results. You can search this Web site at any time.

AVAILABILITY OF INFORMATION

You will receive a copy of this signed and dated consent form.

You will be told about any new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.

WHAT ARE YOUR COSTS TO BE IN THIS STUDY?

There is no cost to you or your insurer/third party payer for participation in this study.

WILL YOU BE PAID TO PARTICIPATE IN THIS RESEARCH STUDY?

{This section should include any and all forms of reimbursement, incentives or compensation.}

After completion of the 6 weeks of therapy, you will be given \$50, to help with transportation and parking.

WHAT COMPENSATION IS AVAILABLE IN CASE OF INJURY?

{This section should be modified in accordance with your institutional policy (-ies).}

It is important that you promptly tell the researchers if you believe that you have been injured because of taking part in this study. You can tell the researcher in person or call him/her at the number listed at the top of this form.

In the event that you become ill or injured from participating in this research study, emergency medical care will be provided to you. University of California Irvine will decide on a case by case basis whether to reimburse you for your out of pocket health care expenses.

WHAT ARE YOUR RIGHTS AS A PARTICIPANT?

You may choose either to take part or not to take part in this research study. If you decide to take part, you may decide to leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to you.

The investigators will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

If you have questions about the study, you will have a chance to talk to one of the study staff or your regular doctor. Do not sign this form unless you have had the chance to ask questions and have received satisfactory answers.

Nothing in this consent form waives any legal rights you may have nor does it release the investigator, the sponsor, the institution, or its agents from liability for negligence.

HOW WILL INFORMATION ABOUT YOU BE KEPT PRIVATE AND CONFIDENTIAL?

Every effort will be made to maintain the confidentiality of your medical and research records related to this study. All identifiable information that will be collected about you will be removed and replaced with a code. A list linking the code and your identifiable information will be kept

separate from the research data. All research data will be maintained in a secure location at University of California Irvine. Only authorized individuals will have access to it. All research data stored electronically will be on a secure computer with password protection. The researchers intend to keep the research data for approximately 5 years after the research is published. Your data will remain password protected on a secure computer in a locked room in a locked building, and in a locked file cabinet in the same room.

Agents of the NIH StrokeNet National Data Management Center, the sponsoring Investigator Dr. Steven Cramer, and the StrokeNet CIRB will be granted direct access to your original medical and research records for verification of clinical trial (research study) procedures or study data, without violating your confidentiality, to the extent permitted by the applicable laws and regulations. By signing this consent form, you are authorizing such access. The data from the study may be published; however, you will not be identified by name. Your identity will remain confidential unless disclosure is required by law.

We may submit information about you to a data repository. A data repository is a large database. Information from many research studies is stored and managed in the repository. All of your personal identifiable information (PII) would be removed from your information. This includes your name, address, and phone number. The information is only identified with a unique code. The code consists of numbers and letters [for example: 1A462BS]. This code is known as a Global Unique Identifier (GUID). Researchers may collect and share the information with each other to study stroke prevention, treatment and recovery in the future. PII will not be provided to any researchers using your information.

Authorization to Use and Disclose Health Information

{This section should be modified in accordance with your institutional policy (-ies).}

A federal regulation known as the Privacy Rule gives you certain rights concerning the privacy of your health information. Researchers covered by this regulation are required to get your authorization (permission) to use and disclose (share with others) any health information that could identify you. You should have received a Notice of Privacy Practices when you received health care services here. If not, let us know and a copy will be given to you.

If you sign this informed consent form, you are giving permission for the use and disclosure of your health information for purposes of this research study. You do not have to give this

permission. Your health care outside of the study, payment for your health care, and your health care benefits will not be affected if you choose not to sign this form. However, if you do not sign this form, you will not be able to participate in the study.

Who Will Use and Disclose My Health Information? The study doctor and research staff (the study team) may use your health information to conduct, review, and determine the results of the study. The study team may also use your information to prepare reports or publications about the study. However, your name will not appear in any report or publication without your permission.

What Health Information will be Used and Disclosed? The study team will record your medical history, the treatment you receive, and the results of examinations and tests done during the study on study forms. The study team will send the completed study forms to the study sponsor. Representatives from the groups identified below may need to look at your medical records to make sure that the information on the study forms is correct or that the study was conducted properly. Your medical records may include other health information about you and may include documents that directly identify you. Reviews like that will take place at the study center or where the medical records are stored and can take place after the study is over.

Who Will Receive My Health Information? Your study information or medical records (as described above) or both may be shared with the following people or groups:

- The study sponsor or its representatives, including companies it hires to provide study-related services
- Researchers who are conducting this study at other study centers
- The StrokeNet Central Institutional Review Board and any other committees responsible for overseeing the research
- StrokeNet Central Institutional Review Board Human Research Protection Program staff
- Research site employees providing service or care to you
- The StrokeNet National Data Management Center (NDMC), housed in the Data Coordination Unit (DCU) in the Department of Public Health Sciences at the Medical University of South Carolina (MUSC)
- Federal and State agencies, such as the U.S. Food and Drug Administration (FDA), Department of Health and Human Services (DHHS), the National Institutes of Health (NIH), and other US and non-US government bodies that oversee or review research

Will My Information be Protected by the Privacy Rule After it is Disclosed to Others?

Research site employees at {INSERT LOCAL SITE NAME} are required by the Privacy Rule to protect your health information. After your information is shared with others, such as the study

sponsor, it may no longer be protected by the Privacy Rule. The people who receive this information could use it in ways not discussed in this form and could disclose it to others. The sponsor will use and disclose your information only for research or regulatory purposes or to prepare research publications. In addition to using it for this study, the sponsor may reanalyze the study data at a later date or combine your information with information from other studies for research purposes not directly related to this study. The goal of any such research would be to learn more about drugs or diseases or to help design better studies in the future. When using your information in these ways, the sponsor may share it with regulatory authorities, other researchers, its business partners, or companies it hires to provide research-related services.

What Happens if I Leave the Study Early? If you stop participating in the study early for any reason, the study team will tell the sponsor why. If the study team asks you to come to any more study visits and you agree, the study team will send the sponsor information from those visits as well. All information collected about you may continue to be used and disclosed.

Will My Authorization Ever Expire? This Authorization does not have an expiration date. The study team may need to correct or provide missing information about you even after your study participation is over and a review of your medical records may also take place after the study is over.

May I Take Back My Authorization? You have the right to take back (revoke) your Authorization at any time by writing to the person in charge of this research study whose information is listed on the front of this form. If you revoke your Authorization, the study team will not collect any new health information about you. However, they can continue to use and disclose any already-collected information if that is necessary for the reliability of the study. The sponsor can also still keep and use any information that it has already received. If you revoke your Authorization, you can no longer continue to participate in the study.

May I Look At My Study Information? You have a right to see and make copies of your medical records. However, to ensure the reliability of the study, you will need to wait to see your study records until the study is completed.

WHO DO YOU CALL IF YOU HAVE QUESTIONS OR PROBLEMS?

If you have questions, concerns, complaints and/or suggestions about this research study or to report a research-related injury, please contact the researcher.

{INSERT TEXT HERE}

{INSERT TEXT HERE}

Local Principal Investigator Name

Telephone Number

You can also Call the StrokeNet CIRB at 513-558-5259, Monday-Friday 8am-5pm EST if you:

- Think the research has hurt you.
- Have general questions about giving consent or your rights as a research participant in this research study.
- Have questions, concerns, complaints and/or suggestions about the research.
- Cannot reach the research team or you want to talk to someone else.

To report complaints or concerns to an independent agency in an anonymous and confidential manner, please call the Research Compliance Hotline at 1-800-889-1547.

CONSENT TO PARTICIPATE IN A RESEARCH STUDY**Study Title:****UC IRB Study #:****Sponsor Name:** Steven C. Cramer, MD
NINDS/NIH**Investigator Information:**

Steven C. Cramer, MD

Principal Investigator Name

{INSERT TEXT HERE}

Local Site Name

{INSERT TEXT HERE}

{INSERT TEXT HERE}

Local Principal Investigator Name

Telephone Number 24 hr Emergency Contact

I have read or someone has read to me, this Informed Consent Document which describes the purpose and nature of this research. I have had time to review this information and have been encouraged to ask questions. If I do not participate or if I discontinue my participation, I will not lose any benefits or any legal rights. My participation in this research is completely voluntary. I have received (or will receive) a copy of this signed and dated form for my records and future reference. I have been given the information about the use and disclosure of my health information for this research study.

I give my consent to participate.

Participant

Date

PERSON OBTAINING CONSENT

I have read this form to the participant and/or the participant has read this form. An explanation of the research was given and questions from the participant were solicited and answered to the participant's satisfaction. In my judgment, the participant has demonstrated comprehension of the information.

Signature and Title of Person Obtaining
Consent and Identification of Role in the Study

Date

APPENDICES: 2. FOOD AND DRUG ADMINISTRATION STATEMENT OF NON-SIGNIFICANT RISK

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center – WO66-G609
Silver Spring, MD 20993-0002

September 30, 2014

Steven C. Cramer, MD
Professor
UC Irvine Medical Center
200 South Manchester Ave., Suite 206
Orange, CA 92868

Re: Q140628 – Study Determination for the Proposed Study titled, “Telerehabilitation for Patients with Stroke”
Dated: May 27, 2014
Received: May 28, 2014

Dear Dr. Cramer:

The Food and Drug Administration (FDA) has reviewed your submission, dated May 27, 2014, requesting a risk determination for the proposed study titled, “Telerehabilitation for Patients with Stroke.”

FDA has determined that your proposed clinical investigation is a nonsignificant risk (NSR) device study because it does not meet the definition of a significant risk (SR) device under § 812.3(m) of the investigational device exemptions (IDE) regulation (21 CFR 812).

An IDE application is not required to be submitted to, or approved by, FDA for a NSR study. A NSR study is, however, subject to the abbreviated requirements described in § 812.2(b) of the IDE regulation. The abbreviated requirements stipulate that the sponsor of the investigation must label the device in accordance with § 812.5; obtain institutional review board approval of the investigation as a NSR study; ensure that each investigator obtains informed consent from each subject under the investigator’s care; comply with the monitoring requirements of § 812.46; maintain records required under § 812.140(b)(4) and (5) and file the reports required under § 812.150(b)(1) through (3) and (5) through (10); and ensure that participating investigators maintain the records required by § 812.140(a)(3)(i) and file the reports required under § 812.150(a)(1), (2), (5) and (7).

Under the abbreviated IDE requirements, a sponsor must also comply with the prohibitions against promotion and other practices as identified in § 812.7. According to this section of the regulation, the sponsor of a NSR study, investigator, or any person acting for or on behalf of the sponsor or investigator is prohibited from promoting or test marketing the investigational device until after FDA has approved the device for commercial distribution; commercializing the device by charging a price greater than that necessary to recover the cost of manufacture, research, development, and handling; unduly prolonging the investigation; and representing the investigational device as being safe or effective for the purposes for which it is being investigated.

APPENDICES: 3. BEHAVIOR CONTRACT TEMPLATE

BEHAVIORAL CONTRACT: Telerehabilitation Group

I, _____, agree to perform the telerehabilitation practice games and exercises on the computer in my home each assigned day, and I will try to adhere to the attached Daily Schedule as reasonably as possible. I agree to use the study computer and equipment placed in my home as directed. I will not unplug, modify, or change this equipment, and I agree not to use it for purposes outside of the study.

I agree to try to use only my affected arm when using the devices for games, even if I had previously been using only my strong arm for some of those tasks. The only time I will use the non-affected arm is when a task is two-handed by its nature and this is what is instructed to me on the computer.

I will not perform any practice, or use any equipment if I feel that my safety could in any way be affected. Safety is always the first consideration.

If I have any concerns about the practice, or laptop/equipment, I will reach out to the study team at one of the video phone calls. If an emergency concern arises, I can call one of the contact numbers that appears on the front page of the consent form.

One major goal for me is that by the end of this study, my arm function will improve for:

Signature of Patient

Signature of Therapist

Date

17_Jan_2014

BEHAVIORAL CONTRACT: In-Clinic Group

I, _____, agree to perform the rehabilitation practice in my home or in the rehabilitation clinic each assigned day, and I will try to adhere to the attached Daily Schedule as reasonably as possible. I agree to use the rehabilitation booklet provided to me in my home as directed.

I agree to try to use only my affected arm in all activities, even if I had previously been using only my strong arm for some of those tasks. The only time I will use the non-affected arm is when a task is two-handed by its nature and this is what is instructed to me by the therapist.

I will not perform any practice, or use any equipment if I feel that my safety could in any way be affected. Safety is always the first consideration.

If I have any concerns about the rehabilitation practice or the exercise booklet, I will reach out to the study team via phone calls or ask during one of my live visits to UC Irvine. If an emergency concern arises, I can call one of the contact numbers that appears on the front page of the consent form.

One major goal for me is that by the end of this study, my arm function will improve for:

Signature of Patient

Signature of Therapist

Date

17_Jan_2014

APPENDICES: 4. RECRUITMENT FLIER**Study to improve arm function after stroke**

Many people who have had a stroke continue to have weakness in an arm. Extra therapy is known to help the arm improve after stroke, but the best approach remains uncertain. This study will examine this issue by comparing therapy provided in a clinic with therapy provided in your home via a computer.

If you had a stroke 4-36 weeks ago and still have weakness in your arm, you might be eligible for this study.

If interested, contact XXXXXX, via

Phone: (XXX) XXX-XXXX

Email: XXXXXXXX

and ask about the "Stroke Study"

For more info on this study, visit: www.clinicaltrials.gov

Participation involves between 4 and 22 visits to XXXXXXX, as well as some therapy in your home. There is no charge to you or your insurance company, and you will be provided \$50 payment for transportation expenses.

APPENDICES: 5. TELEPHONE SCREENING SCRIPT**Telerehabilitation in the Home versus Therapy In-Clinic for Patients
with Stroke**

An assessor-blind, randomized, non-inferiority trial

Phone Screen Script/Form

Name of Subject: _____

Name of person completing phone screen form: _____

Date of phone screen: _____

Hello, I am calling from the _____, may I please speak
with_____.

If available, proceed with script.

If not available,

Do you know when would be a good time to call back to speak with him/her?

If yes, I will try to reach him/her then.

If no, I will try to call back at another time.

If the person states not to call back, no further attempts will be made to contact the individual.

Thank you for your assistance, goodbye

“Hello, my name is _____. I understand that you might be interested in participating in our study related to recovery of the arm after stroke. First I would like to tell you about the study.”

The main purpose of this study is to find out if telerehabilitation is as good as therapy provided in person to help people recover from a stroke. Telerehabilitation allows a patient to use the internet to obtain rehabilitation therapy at home.

This study is sponsored by the National Institutes of Health. The study is directed by Dr. Steven C. Cramer, a researcher at the University of California, Irvine. Medical supervision for this study is provided by Dr. Cramer. 8-12 study sites across the country are conducting this trial.

Dr. _____ is the local investigator at ___Local site_____

If you decide to participate in this study, you will be in the research study for approximately 10-12 weeks. During this time, you would have six weeks of in-clinic therapy or home-based telerehabilitation therapy. During each week of therapy, there will be 6 sessions of therapy per week: 3 of these sessions per week will be supervised and 3 of these sessions per week will be unsupervised. In total, there will be 36 therapy sessions - 18 supervised and 18 unsupervised.

The possible risks and/or discomforts of this study are expected to be minimal. Subjects may experience some fatigue and muscle soreness after moving their stroke-affected arm during rehabilitation practice.

If you are still interested, I need to ask you some questions to determine if you are potentially eligible for the study. These are questions about your health and some questions regarding participation in the study. If at any time you do not like the questions, or do not wish to answer, that is OK - you do not have to answer.

If you are not eligible for the study after today's survey or you are eligible but decide not to participate in the study, we will destroy your answers today.

If you are eligible and decide to participate, your answers will be kept. At your first visit, we will ask you if we may keep the answers that you provided today.

If you are potentially eligible, we will call you back in a few weeks to repeat this survey and will keep your answers until we know whether you are eligible and whether you will participate.

If you do not want us to call you back to repeat this survey, we will destroy your answers today.

Are you ok with proceeding?"

(1) What was the date of onset for your stroke? _____

The subject is 3-35 weeks post-stroke Yes No

(2) What is your contact data?

Home phone _____

Cell phone _____

Other phone _____

Email addresses

Spouse or Domestic Partner phone and email data

Other phone and email data, if relevant (Relative, Friend, other Caregiver)

The subject lives < 25 miles from the clinical site Yes No

(3) What is your date of birth?

The subject is 18 years or older Yes No

(4) Does the subject speak sufficient English to participate in this study? Yes No

(5) Can you commit to visiting the study clinic 18 times over 6 weeks, given that it's a 50-50 chance you will be in this treatment group? Yes No

(6) Can you likely score at least 3 points on the Box & Block Test? To score a point, you will have to grasp an inch-wide block with the hand affected by stroke, lift it off the table 6 inches into the air, and then set it back down onto the table. You could try this using the spoon end of a teaspoon. Yes No

Notes on eligibility Issues:

“Based on your responses, It looks as though you may may not currently be potentially eligible for the study.

If the subject is potentially eligible:

If the subject is potentially eligible and ready to move forward with study participation, set up a date for the subject to come to the site for a Screening Visit.

If the subject is potentially eligible but is not ready to move forward with study participation, set a time to call the subject back to repeat this phone screen.

If the subject is not potentially eligible:

If the subject is not eligible exclusively because the subject is not yet 3 weeks post-stroke, set a time to call the subject back to repeat this phone screen.

If the subject is not eligible because of the Box & Blocks screen, and there is the potential that the subject may improve and thereby become potentially eligible in the future, inform the subject that he/she will be re-contacted regularly, until week 35 post-stroke, if he/she is agreeable to this.

Future Plans:

Date of next planned call to the subject (if not currently eligible, should be 30 days after current date):

Other Actions:
