PROTOCOL TITLE:

Establishing the functional viability and dose-response of Duck, Duck Punch: A Stroke Rehabilitation Computer Game

PRINCIPAL INVESTIGATOR:

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1.0 Objectives / Specific Aims

We developed a prototype Kinect-based post-stroke rehabilitation game called **Duck Duck Punch (DDP)**. The **overall goal** of this NIH Small Business Initiated Research (SBIR) Phase II project is to determine its functional viability and dose-response.

This goal will be achieved by conducting three studies (thus requiring 3 informed consent forms).

Study 1: DDP Intervention

Aim 1: Evaluate whether home use of DDP for 6 weeks improves post-stroke arm motor ability.
Rationale: In our preliminary studies, we demonstrated that stroke survivors feasibly used DDP to self-direct high-repetition arm movement sessions. However we do not know if the observed gains in arm motor skills could be attributed to DDP (custom designed) versus a commercially available, "off the shelf" computer game. *Hypothesis:* The unique design of DDP elicits healthy movement repetitions at an optimal level of challenge therefore, will yield greater gains in post-stroke arm ability when compared to a commercially available "off the shelf" computer game that may elicit un-healthy movement patterns and/or lower amounts of movement repetitions. *Design:* Single blind, parallel-arm with blocked randomization according to motor impairment level. **N=66** subjects with primary diagnosis of post-stroke arm paresis will participate in dose-matched, self-directed, in-home play of either (1) DDP or (2) a commercially available computer game over 6 weeks. *Analysis:* Between-group comparison of pre- to post- changes in arm movement abilities for each impairment strata.

Aim 2: Examine the dose-response relationship by relating movement repetitions to arm motor skills.
Rationale: Commercialization of this product requires an understanding of the dose-response relationship across different levels of stroke severity to guide treatment programs. *Design:* Segmented regression and growth mixture models will be used to relate the number of arm movement repetitions to treatment response in patient subgroups separated by level of motor impairment.

Study 2: Focus Groups

Aim 3: Determine the treatment validity of the DDP report as a measure of impairment and response.
Rationale: Functional viability requires that DDP be relevant to the post-stroke recovery process. At the end of each DDP session, a report summarizes impairment measurements made with the Kinect. It is not known if this report is useful (valid) for informing treatment decisions across the rehabilitation continuum. *Design:* DDP is currently being used in several in- and out-patient stroke rehabilitation facilities. For this study, we will obtain feedback from focus groups of (1) therapists (2) survivors who have played DDP and (3) caregivers of those who have played DDP regarding the validity of the DDP report to inform treatment decisions. Information gained from these consumer focus groups will inform re-design of the DDP report to make it more clinically relevant and useful.

Impact: There is a need to develop and market new options for extended post-stroke arm movement practice. This project will yield data regarding DDP's effect on recovery, dosing, and the translatability of its performance report. Thus, this Direct-to-Phase-II SBIR will set the stage for a future definitive study to enable clear decisions regarding the clinical utility and commercialization of DDP to therapists and stroke survivors.

Study 3: Joint Range of Motion Validation

In addition, a small, third study will be conducted; its Aim is to **validate a new method of measuring shoulder and elbow joint ranges of motion**. This new method involves using the Microsoft Kinect to track arm motion. We have written new software codes to calculate joint ranges of motion using Kinect recordings of arm motion, we expect that these new codes provide accurate measurements, but have no evidence to support our expectation. Therefore, for this 3rd study we will enroll 10 neurologically healthy individuals and 10 individuals with stroke (at the conclusion of the parent study) for a single 1-hour evaluation session in which the Kinect joint angle measurements will be compared to the same joint angle measurements made with our state of the art laboratory-based PhaseSpace Motion Capture (MoCap) system. This 3rd study will have its own informed consent. The concurrent validity of the Kinect and MoCap measures will be studied with intraclass correlational analyses. If the Kinect-based measures are similar to the MoCap measures (within an acceptable 10 degree measurement error), then the Kinect measures will be incorporated into the outcomes of the parent study.

Study 4: E-learning for At-Home Paretic Arm Use

Aim 4: Test the feasibility of an e-learning module to elicit patient self-directed paretic arm use in their home

Rationale: Results from recently concluded large stroke rehabilitation clinical trials clearly indicate a disparity between paretic arm use during (1) therapy vs. (2) at home or in the community. That is, patients safely accomplish hundreds of paretic arm movement repetitions during a structured therapy session. Yet, they fail to translate motor skills from clinic to home. As documented by wrist-worn activity monitors, patients rarely move the paretic arm during non-structured (non therapist initiated) real-world home/community activities despite having had intensive in-clinic arm rehabilitation. Reasons for this disparity include patients' self-reported lack of knowledge regarding optimal ways to care for him/herself after therapy has ended. It is likely that the current therapy model of in-clinic therapist-guided arm movement practice inhibits patients' development of self-management skills by reinforcing reliance on the therapist's guidance for arm use. Thus, patients leave therapy without the skills to self-direct their own long term recovery. That is, they do not know how to, on their own, overcome the challenges to using their paretic arm during real world activities at home and in the community. In efforts to address this problem, we created an online learning module within MUSC's Moodle e-learning platform for stroke survivors designed to **bridge the gap between the clinic and home**. The purposes of this e-learning module are to (1) provide information about stroke motor recovery to elicit cognitive learning for self-management and (2) coach stroke survivors during at-home paretic arm use via therapist-patient teleconferences to elicit psychomotor learning for self-management.

Design: This is a **proof of concept** study to ascertain the **feasibility** of stroke survivors ability to access and benefit from the Moodle e-learning module.

Impact: if proven feasible, these data will support a future, properly powered clinical trial to test the e-learning module's impact on stroke patients' self-management skills. At the current time, e-learning is not used to bridge the clinic-to-home transition in stroke rehabilitation. Thus, this research is highly innovative, and has the potential to completely transform post-rehabilitation care for stroke survivors.

2.0 Background

Background: Stroke is a problem nationally, but especially in the southeastern USA, a region known as the "stroke belt" where stroke incidence is high and age of stroke onset is low. The vast majority, >75%, of stroke survivors experience paresis of one arm/hand that does not resolve acutely. Long-term arm movement impairment restricts independence with self-care and vocational activities, increases caregiver burden and reduces quality of life. Although rehabilitation improves outcomes, systematic financial

pressures increasingly limit its duration. Unfortunately, this is happening at a time when strong evidence is emerging that traditional therapy programs do not provide adequate amounts of movement practice needed for motor recovery. Thus, there is a need for innovative technology to augment traditional stroke rehabilitation programs in a way that can provide the necessary movement practice within the constraints of current rehabilitation practice.

To meet this need, we developed a prototype Kinect-based post-stroke rehabilitation game called **Duck Duck Punch (DDP).** While maintaining the appeal of a game, DDP has a therapeutic focus because its unique design elicits an arm motor recovery process consistent with evidence-based stroke rehabilitation principles. The player moves his/her physical arm to control an avatar arm to reach and "punch" virtual ducks. Custom features allow tailoring of game difficulty to match a player's impairment level so that the player seeks to accomplish optimally challenging movement goals. By design, the avatar does not respond to atypical arm motions, which encourages the player to trial and error a variety of motions until implicitly learning the more normal strategy. Thus, unlike most commercially available "off the shelf" games, success requires "therapist approved" healthy arm motions. Success motivates continued game play for extended practice of healthy motions. Therapists can integrate DDP into in-clinic or in-home therapies for additional quasi-supervised movement practice and receive a performance report that quantifies and monitors progress toward recovery goals. Further development of this report will enable its integration into a billable rehabilitation program.

A young stroke survivor playing Duck Duck Punch.

We licensed DDP and formed a company, Recovr, which has received investment funding for initial start-up and market research. Of note, DDP has also received FDA 510(k) Clearance to *"support physical rehabilitation of adults in the clinic and at home via performance of therapist-assigned reach exercises for the upper extremities."* In a funded NIH/NIGMS CTR pilot project, we established the technical merit and feasibility of DDP as a tool to augment inpatient, outpatient and home-based stroke rehabilitation by increasing therapist- and patient-directed movement practice opportunities. Very promising results motivated the current project that seeks to test the functional viability of DDP and determine its commercial potential.

A. SIGNIFICANCE

A.1. Stroke incidence in rural southeastern states is high, and age of stroke onset is low, thus burdening the region. The southeastern US states is known as the "stroke belt" where stroke incidence is unusually high and the age of stroke onset is unusually low.[1] The overwhelming majority of stroke survivors, >75%, exhibit **upper extremity (UE)** hemiparesis, and only 15% will recover fully.[2, 3] Residual UE impairment is closely linked to long-term disability[4] and reduced quality of life.[5] With such a large cohort of young disabled stroke survivors, there are significant financial and resource burdens on healthcare throughout the region.[6]

A.2. Rehabilitation can reduce stroke-related disability by improving UE movement skill. Decades of research in neuro- and rehabilitation science provides clear evidence of the potential for recovery, even many years after stroke.[7-9] The existing data strongly suggest that the damaged brain possess remarkable ability to reorganize neural networks contributing to functional recovery.[10] Stroke rehabilitation provides behavioral training to harness learning-dependent neural plasticity and promote functional UE motor skill recovery.[9, 11]

A.3. UE motor recovery requires substantial practice of appropriately challenging movement tasks. High numbers of movement repetitions drive neural reorganization in areas of the brain associated with improved skills.[12-14] However, the greatest neuroplastic changes are associated with the repetition of new, progressively more challenging, skills rather than repetition of existing skills.[15, 16] Repetitive practice of "new" motor skills means practicing movements for which an individual has partial but not complete

success, or, said differently, practicing movements that are neither too easy nor too difficult. Practice at the "just right" level of challenge optimizes the sensorimotor feedback available for learning by offering opportunity for implicit error detection and motor strategizing.[17] This also means that the level of challenge must progress as the individual's skill level increases.[17, 18]

A.3. Stroke patients do not receive enough UE movement practice. There has been a failure to translate evidence-based guidelines into stroke rehabilitation. For example, several hundred movement repetitions/day are required for neural reorganization and behavioral change,[14] however current stroke rehabilitation programs include ~32 movement repetitions/day.[19] Therapy is further under-dosed because inpatient rehabilitation length of stay is usually capped at 15-20 days,[20] with most patients receiving a total of ~20 sessions each lasting ~30 minutes.[21] Young working-age stroke survivors, a group without uniform healthcare coverage, may have even shorter lengths of stay and less opportunity to practice. Furthermore, access to outpatient therapy is poor, especially in rural southeastern states like South Carolina, where >75% of the population must drive >30 minutes for specialized stroke services.[22, 23] Clearly, there is a need for cost effective, high-dose, appropriately challenging UE movement rehabilitation options to reduce stroke disability and burden in this region.

A.4. Interactive virtual reality technology can provide low-cost opportunities for UE movement practice. Virtual reality technology offers exciting possibilities for low-cost, accessible, and highly motivating therapy options to address the need for evidence-based doses of movement practice.[24-27] Gaming systems are divided into two categories; custom designs (e.g., Duck Duck Punch) or commercially available "off the shelf" systems.[25, 28, 29] Gaming-assisted stroke rehabilitation is a young, rapidly growing field. Our team is comprised of experienced technology developers[30-33] and stroke rehabilitation therapists.[34-37] We argue that this partnership will ensure that technology developed by Recovr complements evidence-based practice by maintaining a therapeutic focus while remaining engaging.[38, 39]

B. INNOVATION

B.1. We developed, and licensed an innovative stroke rehabilitation game; *Duck Duck Punch*. We

are among the first research teams with expertise in *both* stroke rehabilitation and computer science to leverage Microsoft Kinect skeletal tracking technology for retraining post-stroke UE movements.[40] Duck Duck Punch (DDP) is an interactive game with an old time carnival theme. The patient sits in front of the Microsoft Kinect and controls a virtual arm with his/her physical arm; reaching forward to "punch" virtual ducks. Custom features enable patients with all levels of impairment to play. Success motivates continued play, so that the user engages in high-repetition UE movement practice. Microsoft recognized our innovation when they awarded DDP 2nd place worldwide in the prestigious 2012 international Imagine Cup competition held in Australia. Impressively DDP stood out from a field of over 500 worldwide applicants, all of whom had proposed novel uses of the Kinect for healthcare.

B.2. Why does the (very busy) field of rehabilitation computer gaming need DDP? DDP is unique because its design integrates scientifically based principles of post-stroke motor recovery. Specifically, DDP is uniquely designed to retrain a healthy movement pattern (forward reach) by constraining compensatory (atypical) trunk motions that may interfere with recovery. This is important because stroke impairs forward reaching skills. Instead of reaching forward by moving the arm away from the body by simultaneously extending the elbow and flexing the shoulder, patients inadvertently pull the paretic arm towards the body, i.e., the pathological "flexion synergy" characterized by simultaneous elbow flexion and shoulder abduction/extension.[41] When forward reach is impaired, individuals with stroke compensate by leaning forward to transport the hand to an object.[42] Elbow extension motion is inversely related to trunk compensations.[43] The ability to reach forward without compensation is an important indicator of recovery as it marks the threshold between categories of severe and moderate impairment[36] and predicts quality of life.[44]

Current evidence-based rehabilitation principles specify that motor rehabilitation should promote recovery of healthy not compensatory movement patterns because compensatory trunk/arm movements are associated with maladaptive plasticity,[45] shoulder pain,[46] and reduced potential for long term recovery.[47] Therefore there is a need to retrain forward reach while discouraging trunk compensations. DDP specifically designed so as to assure that it elicits an arm movement pattern consistent with current evidence based principles of rehabilitation . Specifically, DDP is designed to constrain compensatory (atypical, unhealthy) trunk motions because the DDP shoulder avatar is fixed in space meaning that the avatar arm does not respond to patients' attempts to use compensatory trunk motion to "punch" the target rather than reach forward with the arm. As shown in Figure 1, the avatar hand moves toward the target only when patient reaches forward using shoulder flexion-elbow extension not when he/she leans forward. Therefore, when a more "normal" strategy is used, the patient experiences the reward of successful game play to reinforce the movement strategy.

Figure 1: A subject enrolled in the pilot study. On day 1 (left) she continually attempted to lean forward to bring the avatar hand to the duck, however the avatar arm did not respond. On day 5 (right) she had implicitly (re)learned a more normal movement strategy.

In the very busy field of computer gaming for rehabilitation DDP stands out because of its therapist-like focus on training good quality forward reaching movements. Recent systematic reviews[48],[49] show that only 13 studies have utilized the Kinect for stroke rehabilitation. The Kinect is controlled by body or limb motion rather than a controller and therefore is usable by severely impaired individuals who do not have the hand/finger recovery needed to grasp or push controller buttons. To our knowledge, only DDP[40] and 3 others[50-52] track arm motion (rather than the hand) with the Kinect to retrain reaching motions, but DDP stands alone with its focus on healthy movement patterns only.

DDP is designed to so that the difficulty of game play can be adjusted to match patients' level of ability and facilitate post-stroke motor skill (re)learning that underlies recovery.[15, 17] If a task is too difficult, meaning that the patient does not have enough skill to achieve the task goal, the patient will utilize compensatory trunk and/or arm movement strategies.[42, 53] These atypical, poor quality motions, i.e., "learned bad-use"[47] may inhibit overall recovery. Therefore DDP was designed so that the difficulty of game play can be adjusted through (1) avatar arm scaling, shown in Figure 2 and (2) target selection, shown in Figure 3. By matching game difficulty to player's ability DDP allows the person to experience a combination of both errors and success during repetitive practice[54] thereby providing implicit and explicit feedback to challenge the nervous system and promote learning of good quality motions.

Figure 2: Avatar Arm Scaling: During set-up, the Kinect maps paretic UE motion. The grey arm represents actual forward reach. The tan arm is the avatar. The avatar can be scaled so that it has more range of motion than the patient's physical arm to achieve full forward reach, which enables individuals with impaired voluntary range of motion to play DDP.

Figure 3: Target Selection: Reach movements vary in difficulty

B.3. DDP provides rehabilitation options for individuals with moderate-severe UE impairment and very little hand recovery, an underserved group. Only 25% of stroke survivors recover enough hand dexterity to grasp, release and manipulate objects during task practice rehabilitation sessions.[55] This means that the vast majority of stroke survivors do not qualify for "gold-standard"[56] task practice therapies. DDP provides an option for this underserved population (see Figure 4). This makes DDP very different from other computer games that are only appropriate for patients with mild impairment because patients must either grasp a controller (Wii)[57] or utilize full arm range of motion to successfully play.

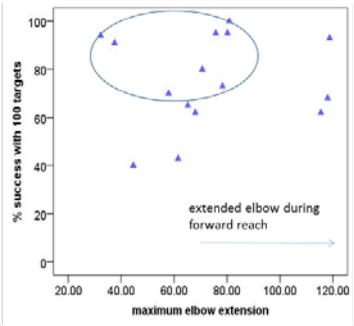


Figure 4: Data collected as the first 15 stroke subjects enrolled in the pilot study describe below played DDP. The data points (blue triangles) in the circle show that subjects experienced >50% success with hitting targets even though they had very limited forward reach (i.e., voluntary elbow extension). The avatar arm scaling described in Figure 2 enabled this success rate.

PRELIMINARY STUDIES

With NIH/NIGMS CTR funding, we conducted a preliminary study aimed at translating DDP out of our research laboratory and into clinical practice settings. Results are summarized here: **N=20 inpatient stroke rehabilitation subjects**, aged 31-78 years and 4-53 days post-stroke enrolled. The aim was to test the safety and usability of DDP in the inpatient rehabilitation environment. We trained subjects' caregivers to set up and operate DDP, and subjects' played during non-therapy hours (evenings/weekends). Subjects self-directed DDP play for 5-7 days, 21 minutes/day, averaging 219 arm movement repetitions/session with no adverse events, reports of pain, and or fatigue that interfered with regular inpatient rehabilitation. **Figure 5** presents data from a representative subject**.** who was 6 days post-ischemic stroke with a baseline Fugl-Meyer Upper Extremity score of 25 (moderate-severe motor impairment). He played DDP while family members operated and coached the session. He engaged in 60-309 arm movement repetitions per day over 6 days, with sessions of 9-28 minutes in duration. At the conclusion, the patient's wife stated; "*we are not computer people, but this was so easy and fun. Can we take it home?"*

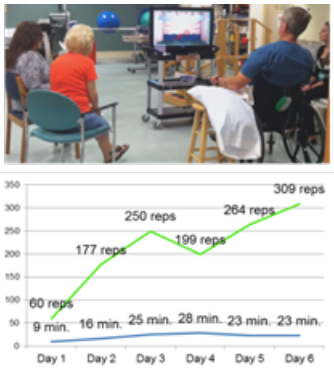


Figure 5: An inpatient 6 days post-stroke played DDP during non-therapy hours.

N=20 community-dwelling stroke survivors were randomized to either DDP or a standard of care home exercise program (HEP). The aim was to document adherence because it is a critical factor contributing to the effectiveness of self-directed home based rehabilitation programs. Subjects and their caregivers randomized to the DDP group were trained to set up and operate DDP, and the control group was trained to carry out shoulder and elbow exercises illustrated in a standard of care HEP. A study therapist phoned all subjects daily. Wrist worn accelerometers documented adherence, defined as days and minutes per day engaged in the activity. In addition, accelerometry data were used to calculate the arm activity ratio, which is a measure of paretic arm use. Higher values indicate greater paretic arm use relative to non-paretic arm use; values close to 1 indicate bilateral arm use. As reported in Table 1, the results were striking; DDP subjects demonstrated statistically greater adherence and paretic arm use.

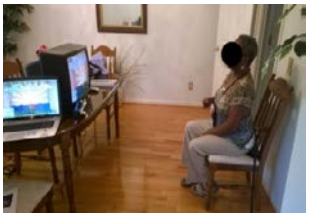


Figure 6: A community-dwelling stroke survivor who played DDP in her home.

	Days engaged range, median	Minutes per day range, median	Arm Activity Ratio range, median
DDP *n=10*	5-7, **7.00**	20.43-96.00, **57.86**	1.49-9.11, **2.85**
HEP *n=10*	0-7, **5.00***	9.00-81.57, **26.82***	1.04-2.42, **1.90***

Table 1: When compared to a standard home exercise program, community dwelling stroke survivors who played DDP exhibited statistically greater (as indicated by asterisks) days and minutes per day engaged in UE movement practice and greater arm activity ratios, indicating higher amounts of paretic arm vs. non-paretic arm movements.

The pilot funding enabled DDP installation at several rehabilitation hospitals: As shown in the photo, we have trained local stroke therapists to incorporate DDP into their rehabilitation sessions for in- and out-patients. We have developed and implemented a ~60 minute DDP training seminar that is eligible as a CEU course for South Carolina occupational and physical therapists. We also have designed a DDP instruction manual that provides detailed instructions for tailoring game difficulty using the virtual arm scaling and target selection features. The manual is continually updated based on therapists, survivors, and caregiver's suggestions. Therapists have accepted DDP into their daily clinical routines and provided overwhelmingly positive support for our pilot work..

Figure 7: An occupational therapist incorporates DDP into a therapy session at a local hospital.

Preliminary Data Motivating Aim 2: In another pilot study we examined the evolution of elbow extension in one participant who played DDP in our research laboratory 2-3 times per week, ~60 minutes per session, for 4 weeks. Kinematic analysis on the first and last day of treatment showed that she gained 28° of elbow extension. However, repeated measures showed that the motor skill acquisition was not linear. Instead, the subject demonstrated progressively less elbow extension (greater flexion) over the first week. Gains in elbow extension did not occur until session 6. These data are interesting because they demonstrate a non-linear dose-response relationship. This subject did not respond to the intervention until she had received approximately 5-6 hours of therapy. This is important information for a therapist or stroke survivor because when deciding how to incorporate DDP into a stroke rehabilitation program, the consumer (therapist or stroke survivor) requires this information to plan the frequency, length and dose of the program.

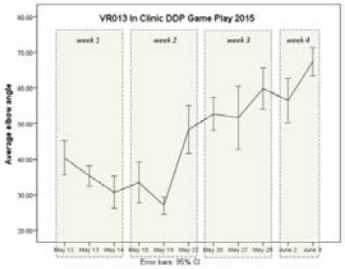


Figure 8: One subject's evolution of voluntary elbow extension over 11 DDP 60 minute sessions. These data suggest a non-linear dose-response relationship thus motivating Aim 2 for the present proposal.

Preliminary Data Supporting the use of a measure of Shoulder-Elbow Interjoint Coordination (IJC) as a primary outcome variable for Aim 2: The new dependent variable for Aim 2 will be shoulder-elbow interjoint coordination (IJC) which will be calculated as the Pearson's correlation coefficient between the trajectories of shoulder elevation and elbow flexion.[53, 58] Joint angles will be obtained through Euler decomposition of the relative segment orientations. Segment reference frames and Euler sequences are defined following ISB guidelines: shoulder elevation as the rotation of the humerus with respect to the thorax along the floating x-axis; elbow flexion as the rotation of the forearm with respect to the humerus along the humerus z-axis.[59] A healthy individual performing a seated reach-to-target task would generate a coordinated increase of shoulder elevation with elbow extension (i.e., decrease of elbow flexion) which would be reflected in a correlation value = -1.00. Values = 0 indicate a decoupling of shoulder and elbow motion, while values = 1.00 represent the shoulder elevation-elbow flexion movement pattern often observed in more severely impaired stroke survivors.

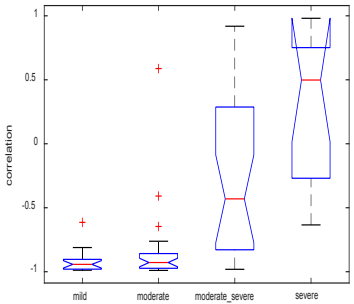


Figure 9: ICJ index (correlation between shoulder elevation and elbow flexion) for a seated reaching task. The horizontal axis indicates stroke impairment level.

1) The IJC can differentiate levels of post-stroke arm movement impairment: N=83 stroke survivors enrolled in an ongoing rehabilitation study were divided into 4 impairment levels according to the Fugl-Meyer Upper Extremity Assessment (FMA-UE) score (out of 60 points)[36]: mild (FMA-UE>47, n=17), moderate (FMA-UE 32-47, n=29), moderate-severe (FMA-UE 16-31, n=29) and severe (FMA-UE<16, n=11). Kinematics were recorded with a PhaseSpace motion capture system while participants performed a seated reach-to-target placed at midline and at 80% of arm's length. IJC was calculated for the time window between the start of reach and the point at which the hand was closest to the target for all subjects. Results shown in **Figure 9**: IJC for mild, moderate,

moderate-severe and severe groups were -0.92, -0.84, -0.26 and 0.28 respectively. A one-way ANOVA showed a main effect ($F(3,79)=22.23$, $p<1E-9$). Post-hoc multiple comparisons with Bonferroni correction showed a significant difference ($p<0.01$) between all impairment levels except between the mild and the moderate group ($p=0.95$).

2) The IJC can be measured by the Kinect: N=4 stroke survivors played DDP in our PhaseSpace motion capture laboratory. We simultaneously collected Kinect and PhaseSpace data while subjects made 10 reaches to a virtual target located at the center of the game window at approximately shoulder height. Shoulder elevation and elbow flexion joint angles were calculated then used to obtain IJC values. **Figure 10** compares shoulder (dotted lines) to elbow (solid lines) joint angle trajectories obtained from the Kinect (black) to PhaseSpace (red) for one subject. Note the similarity between the joint angle trajectories. We then calculated an intraclass correlation coefficient for the IJC obtained from the two systems for each reach. **Figure 11** shows the similar IJC values for subject #4's 10 reaches. When group data were averaged, the IJCs for the 2 systems were strongly correlated ICC=0.94. These data show that the Kinect can reliably and validly measure IJC and therefore this variable can be used as DDP performance measure.

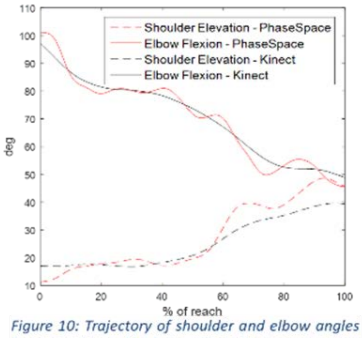


Figure 10: Trajectory of shoulder and elbow angles for one subject. The lines are similar meaning that the angles obtained with the Kinect are similar to those obtained from a "gold standard" motion capture system.

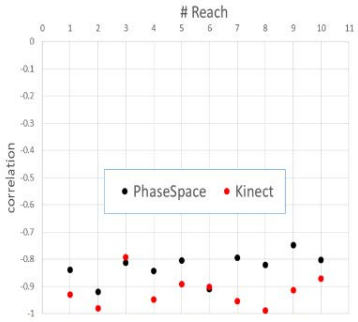


Figure 11: Correlation of the IJC obtained from the Kinect and from the PhaseSpace system, calculated for 10 movements of participant #4.

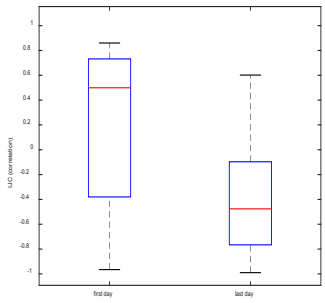


Figure 12: Comparison of the IJC measured while playing DDP at the first and last day of a one-week study

3) The IJC, measured with the Kinect, shows change with DDP game play: N=10 stroke survivors (aged 31-78 yrs, 4-53 days post stroke) played DDP in an inpatient stroke rehabilitation setting once/day x7 days. For every session of playing DDP we recorded the joint positions and segment orientations provided by the Kinect, and used them to calculate the IJC for each successful reach (i.e. each reach that resulted in hitting a virtual target). Data were averaged for the group and compared with a pairwise two-tailed t-test. Results **(Figure 12)** show a significant change in IJC ($p = 0.002$). Subjects also showed reduced upper extremity impairment (FMA-UE scores increased from 33.44 to 39.00, $p=0.06$) and increased motor function (Wolf Motor Function Test time to perform tasks reduced from 46.36 to 30.87 seconds, $p=0.02$) thus suggesting that IJC data collected with the Kinect is a way to monitor participant progress.

4) A change in IJC is related to gains in survivor's self-reported stroke recovery: N=10 stroke survivors played DDP at-home for one week. At the beginning and at the end of the program, we evaluated each participant by administering the Stroke Impairment Scale. IJC was measured with the Kinect. **Figure 13** shows that changes in IJC were significantly correlated to changes in the perceived recovery ($r=-0.71$, $p=0.02$).

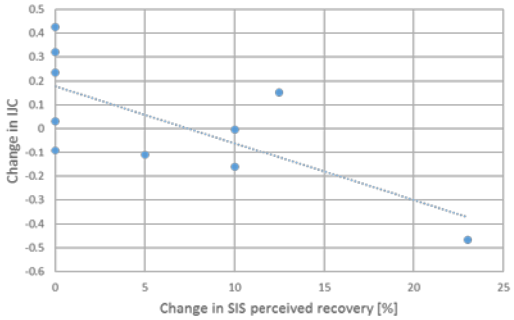


Figure 13: Change in overall SIS perceived recovery is significantly correlated with change in IJC. Negative change in IJC means improvement in coordination thus showing that improved shoulder-elbow coordination related to client self-reports of improved functional recovery.

3.0 Intervention to be studied

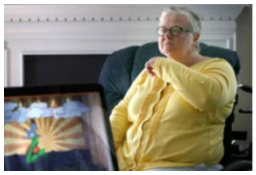
Study 1: DDP Intervention

Aim 1: Evaluate whether home use of DDP for 6 weeks improves post-stroke arm motor ability.
Aim 2: Examine the dose-response relationship by relating movement repetitions to arm motor skills.

- Rationale: Preliminary studies demonstrated that stroke survivors feasibly used DDP to self-direct high-repetition arm movement sessions. However, we did not test its usefulness at facilitating gains in arm motor skills compared to popular commercially available computer games. Commercialization of DDP, a computer game specifically designed for stroke patients, requires an understanding of its effect on post-stroke arm motor ability. Specifically, there is a need to understand how playing DDP may be more/less/equally beneficial as playing an off-the-shelf commercially available computer game.

- Randomization to Treatment Groups: At the pre-treatment visit, after signing informed consent, the Fugl-Meyer Upper Extremity Assessment will be administered (see description below). Its summed score will be the basis for assignment to an impairment strata. Subjects within each stratum will be randomized to play DDP or a commercially available Kinect game, the Kinect Target Shoot.

- Duck Duck Punch (**DDP**): We anticipate that DDP will improve motor skills because the difficulty of the game is matched to the player's level of ability and then continually progressed so that there is an ongoing match between task-difficulty and patient-ability. By continually matching task-difficulty to current patient-ability, we will assure repetition of novel movements, akin to Nudo's "skill training.[16]" Repetition of progressively more challenging movements is associated with greater levels of activity in neural networks supporting motor recovery when compared to repetition of "easy" movements.[60]



- Kinect Target Shooting (**KTS**) was chosen as the comparison because both games require similar shoulder flexion/abduction and elbow extension/flexion movements. This is a commercially available Kinect-based game in the Sports Rivals package. Subjects will remain seated and utilize their affected UE to reach and point at targets. The only way to alter the difficulty of game play is to switch game levels between easy, moderate and expert levels. Although the game is called "target shooting", the player does not hold a physical object in their hand. The "shooting" is accomplished by using one's physical arm to move an on-screen cursor to a target, therefore, similar to DDP, the game can be played by patients who have not recovered hand dexterity.

Kinect Target Shooting: screen shot from a Microsoft marketing video

- Rationale for comparison of DDP to an "off the shelf" commercial game: We custom designed DDP with a focus on forward reaching movement quality because, by design, it does not reward (i.e., constrains) compensatory atypical motions that may interfere with recovery. We expect that subjects will be utilize compensatory motions when playing the commercially available KTS because it does not focus on movement quality. Subjects will be able to use atypical trunk or arm motions to play. This study is important because it is unknown if custom games like DDP actually are more effective at promoting recovery when compared to commercial games.[48] It is possible that an "off the shelf" computer game is just as, or more effective at promoting motor recovery. If so, then there will be no need to continue to develop or commercialize DDP.

- Rationale for comparison of DDP to another computer game rather than rehabilitation therapy: We chose to compare DDP to a commercial game rather than a standard of care therapy because enrolled

subjects will be at least 6 months post-stroke meaning that most will have completed their rehabilitation. As found in the EXCITE trial, less than 50% of the "usual and customary care" group who were an average of 6 months post-stroke, were participating in rehabilitation.[9] We believe that the current standard of care at this time point post-stroke is a home exercise program (HEP) with little, if any, "regular" in-person therapy involving regular contact with a therapist. Home exercise programs are usually written and illustrated handouts[61] although commonly provided, with notoriously low adherence[62] in spite of the fact that stroke survivors understand the importance of [63] and know they should be motivated for home exercises. [64] Our preliminary study results compared DDP to a standard of care HEP. The results were consistent with the literature and clearly showed subjects in the HEP group had low adherence. We seek to compare DDP to another intervention with similar amounts of activity, i.e., an "active" control, so as to understand the effects of our custom game, with its focus on forward reach vs. another game that requires similar arm motions to play.

- Dose: Dose will be matched across groups. All subjects will engage in **18 days (3 days per week over 6 weeks)** of DDP or the commercially available game. All subjects will be instructed to play the game for **60 minutes/day**. It is likely that some subjects will choose to distribute this dose throughout a day. To assure matching does, custom software will be loaded onto the laptop that displays and records the duration of game play as it accumulates over a 24-hour period. Subjects will be instructed to "play the game until the timer shows that you have been playing for 60 minutes in a day."

- Rationale for the Dose: We chose this dose because it is similar to post-stroke arm rehabilitation programs having distributed practice schedules. For example, modified constraint therapy consists of 15 total hours of treatment; 30-minute sessions, 3 days/week for 10 weeks.[65] Similarly, UE functional task training consists of 18 total hours of treatment; 1 hour sessions, 3 days/week for 6 weeks.[66] and impairment oriented training consists of 20 total hours of treatment; 1 hour sessions, 5 days/week for 4 weeks.[67] Because some participants may not be able/ may not choose to complete 60 minutes each day, the intensity of training (averaged amount of time per day) will be added as a covariate to the primary analysis.

Study 2: Focus Groups:

No intervention.

Study 3: Joint Range of Motion Validation: No intervention

Study 4: E-learning Intervention

Aim 4: Test the feasibility of an e-learning module to elicit patient self-directed paretic arm use in their home

Rationale: There is a need to empower stroke survivors' post-rehabilitation skills for self-managing their own long term arm recovery. We created an e-learning module on MUSC's Moodle e-learning platform for stroke survivors designed to **bridge the gap between the clinic and home**. The purposes of this e-learning module are to (1) provide information about stroke motor recovery to elicit cognitive learning for self-management and (2) coach stroke survivors during at-home paretic arm use via therapist-patient teleconferences to elicit psychomotor learning for self-management.

The e-learning course: Subjects will participate in a 4-week online course offered in MUSC's Moodle Platform. Each week the course will offer a/an:

(1) Lesson: The purpose of the weekly lessons are to provide subjects' with information about stroke and stroke recovery. Lessons will include videos, readings, and/or Panopto-recorded lectures from a research team member (or other stroke rehabilitation expert). For example, subjects will learn

principles of activity dependent neural plasticity in order to motivate them to use the paretic arm more and discourage over use of the non-paretic arm.

(2) Asynchronous discussion: The purpose of weekly discussions are to enable subjects to gain a deeper understanding of the week's lesson and begin to apply the lesson to his/her own goals. The asynchronous discussion will occur via the course Discussion Board and be moderated by study team members.

(3) Video teleconference meeting between the group of subjects and the study's occupational therapist. The teleconference, conducted using Web-x within the Moodle course, will allow subjects to interact with each other and the therapist. They will discuss their own arm use goals, receive tips/pointers from the therapist for implementing home arm use, and engage in peer support with other survivors who are also seeking to use their paretic arm more.

4.0 Study Endpoints

Study 1: DDP Intervention

- Primary Outcome Measures:

  - The **Fugl-Meyer Upper Extremity Assessment (FMA-UE**) is a 33 item measure of upper extremity (UE) impairment; however, the 3 items testing reflex response will not be administered because they do not measure a voluntary movement construct.[37] Each item will be scored on a 3 point rating scale (0=unable to perform, 2=near normal performance), item ratings will be summed and reported out of 60 points so that larger numbers indicated less UE impairment.

  - The **Wolf Motor Function Test (WMFT)** is a 15 item measure of UE functional ability. Performance of each item will be timed (seconds) and the average time to perform items will be reported so that lower values indicate greater UE function.

  - **Two kinematic variables** will quantify the effect of the intervention on UE motor skills; (1) **shoulder flexion-elbow extension interjoint coordination** and (2) **trunk displacement**.[43] Kinematic data will be collected from 2 motion capture systems: (1) a PhaseSpace motion capture system in the research laboratory and (2) the Microsoft Kinect, a skeletal tracking sensor that used to operate DDP.

  - *Laboratory based kinematic analysis:* Subjects will be seated on a backless stool in a standardized starting position. Using their affected UE, subjects will perform 2 trials of "reach as fast as you can to grasp (or touch) the soda can." The can will placed on a table at 80% of arm's length at midline, a location affording maximum shoulder flexion and elbow extension.[68] Table height will be adjusted for each individual and no trunk constraint or arm support will be provided during testing. Kinematic data will be recorded with a 10-camera PhaseSpace motion analysis system at a sampling frequency of 240 Hz. Data will be smoothed with a 4th order Savitky-Golay filter (acting on a 200 ms window) and numerically differentiated to obtain marker velocities. A custom kinematic model consisting of 9 segments (pelvis, thorax, head, upper arm, forearm and hand) and with 54 degrees if freedom will be fitted to marker data using Matlab functions. Segment reference frames will be defined according to ISB guidelines.[59] The velocity magnitude of a marker positioned above the base of the third metacarpal bone will be used to define start and end of the movement. Reach start will be defined as the instant when wrist velocity increases above 10% of its peak value, and reach end as the instant when it falls below the same threshold. Joint angles will be calculated through Euler decomposition following ISB guidelines. Shoulder flexion will be defined as the rotation around the z-axis between upper arm and thorax, and elbow flexion-extension as the

rotation around the z-axis between forearm and upper arm. Trunk displacement will be calculated as the displacement of a marker placed at T-10.

- *Microsoft Kinect based kinematic analysis:* The Microsoft Kinect is a skeletal tracking sensor and therefore calculates the user's body segments locations in 3-dimensional space (relative to the sensor). We have created a custom software program that translates Kinect body segment data into joint coordinates which then can be used to calculate kinematic variables. Analyzing motion with the Kinect will allow us to follow the day-by-day progression of each participant as he/she recovers arm movement. The procedure is as follows: at the beginning of each DDP or KTS intervention session, the program will guide participants through a standardized assessment of forward reach. We will calculate the shoulder and elbow joint angles from the recorded kinematic data by post processing it with custom Matlab software.

- Secondary Outcome Measures:

  - The impact of the intervention on "real world" arm use will be assessed with the **Stroke Impact Scale (SIS) Hand and Perceived Recovery** subtests. The SIS-hand consists of 5-items regarding difficulty of paretic hand use during everyday tasks (i.e., picking up a dime, carrying a heavy object) during the previous two weeks. Items will be rated on a 5-point scale (5=not difficult, 1=cannot do) and reported as an average item rating, so scores approaching 5 represent less difficulty. The SIS-recovery subtest is a single-item in which the participant rates his/her perceived post-stroke recovery from 0%-100% recovered.

  - Self-report scales such as the SIS could be limited by recall-bias, therefore **accelerometry** may provide a more accurate assessment of the intervention's impact on real-world arm use.[69-71] During the baseline training session subjects will be shown how to don small Actigraph triaxial accelerometers on the dorsal aspect of each wrist just proximal to the wrist joint. Subjects will be instructed to don and wear the accelerometers for two days during the first week and two days during the final week of the program. The accelerometers will be programmed to collect data at 100 HZ summarized over 1 minute epochs. Raw data will be downloaded when the device is returned at the end of the study. We will use these data to calculate a two Arm Activity Ratios (AAR) for each subject (first week, final week). This variable is calculated by creating a ratio of paretic to non-paretic accelerometer data (i.e., "activity counts").[72] The AAR is an often used UE accelerometer variable,[69, 73] having a high correlation with an assessment of self-reported paretic arm use for daily activities[71] which suggests that the AAR it is a valid method for assessing arm activity in the home environment. An AAR value of 1 indicates that both UEs were used equally as would occur during a bimanual task. A value >1 indicates greater use of the affected UE during the task.

Study 3: Joint Range of Motion Validation

- *Microsoft Kinect based kinematic analysis:* As described above (Aim 1) the Microsoft Kinect is a skeletal tracking sensor and therefore calculates the user's body segments locations in 3-dimensional space (relative to the sensor). We have created a custom software program that translates Kinect body segment data into joint coordinates which then can be used to calculate kinematic variables. Recently, we wrote new software codes to measure elbow and shoulder joint angles with the Kinect. We expect that these new codes are more accurate than the currently used codes. The purpose of this study is to investigate this expectation.

- *Laboratory based kinematic analysis:* As described above (Aim 1) we will utilize our PhaseSpace Motion Capture (MoCap) system to collect arm motion data. Our MoCap system is considered the "gold standard" instrument with which to measure joint ranges of motion. MoCap data are analyzed with a state of the art biomechanical model according to industry standards. The Kinect measures

will be made concurrently and thus allow direct comparison in order to understand how similar (valid) Kinect-based measures are to MoCap measures.

Study 4: E-learning for At-Home Paretic Arm Use

- Feasibility will be assessed
  - Quantitatively by documenting the effect of the e-learning module on subjects' arm motor ability, self-reported arm use at home, and self-efficacy as defined by the following standardized assessments administered before and after the 4 week learning module:
    - **Fugl-Meyer Upper Extremity Assessment (FMA-UE**) as described above.
    - **Stroke Impact Scale (SIS) Hand and Perceived Recovery** subtests as described above.
    - The A **Self-Efficacy Questionnaire** as described above.
    - A Stroke Knowledge Exam which will test the survivors' understanding of stroke and stroke recovery.
  - In addition, we will document
    - The primary problems (if any) that subjects report having with accessing the course.
    - Subjects' anecdotal comments/narrative made to study staff about their experiences using the course.
  - Qualitatively by informally analyzing the discussion board posts for themes that indicate the feasibility of the course (e.g., challenges subjects have with course access), subjects' satisfaction with the course, and content that subjects say is meaningful.

5.0 Inclusion and Exclusion Criteria/ Study Population

Inclusion Criteria

(1) Inclusion Criteria for **Study 1: DDP Intervention:**
  (a) experienced unilateral hemispheric ischemic or hemorrhagic stroke at least 3 months but no more than 7 years prior
  (b) exhibit voluntarily shoulder flexion of the affected arm ≥30° with simultaneous elbow extension ≥20°. We reason that persons at this motor ability level have residual arm activation and enough ability to engage in treatment-related reaching movements elicited by the computer games
  (c) baseline FMA-UE score of at least 19 points but no more than 52 points (out of 60 points) based on our previous published research in which we defined categories of post-stroke UE motor impairment
  (d) passive range of motion in affected shoulder, elbow and wrist within 20 degrees of normal values
  (e) 21-90 years of age
  (f) a caregiver or friend who is willing to assist with the set up and operation of the computer game throughout the 6 week intervention.

(2) Inclusion Criteria for **Study 2: Focus Groups:**
  (a) Subjects with stroke who have played Duck Duck Punch at least 3 time
  (b) The caregiver of someone who has played Duck Duck Punch at least 3 times
  (c) A therapist (occupational or physical) who has utilized Duck Duck Punch in at least 3 treatment sessions.

(3) Inclusion Criteria for **Study 3: Joint Range of Motion Validation**
  (a) Subjects with stroke will be included as per the inclusion criteria identified above (Aim 1)
  (b) Neurologically healthy individuals will be included if they are aged 21-90 (age matched to our stroke sample) and without any neurologic or orthopedic condition that would interfere with shoulder and elbow motion.

(4) Inclusion Criteria for **Study 4: E-learning**
   a. Completed the DDP intervention study described above (Study 1).

Exclusion Criteria

(1) Exclusion Criteria for **Study 1: DDP Intervention:**
   a) lesion in brainstem or cerebellum because lesions in these locations my interfere with the visual-perceptual and cognitive skills needed for motor re-learning as is expected to occur as a result of the intervention
   b) presence of other neurological disease that may impair motor skills (e.g., Parkinson's Disease)
   c) pain in the affected arm that interferes with reaching movements
   d) significant cognitive impairment, defined as Montreal Cognitive Assessment score < 22
   e) orthopedic condition or impaired corrected vision that alters the kinematics of reaching
   a) unable to travel to the UE Motor Function Laboratory in Charleston SC 4 times (pre-, mid- post- and retention testing).

(2) Exclusion criteria for **Study 2: Focus groups:**
   a) Non-English speaking.

(3) Exclusion Criteria for **Study 3: Joint Range of Motion Validation**
   (a) Subjects with stroke will be excluded as per the exclusion criteria identified above (Aim 1)
   (b) Neurologically healthy individuals will be excluded if they have a neurologic or orthopedic condition that interferes with shoulder and elbow motion such as previous fracture, rotator cuff tear, stroke, spinal injury.

- The study sample shall be inclusive of the general population of adults with stroke-related arm motor impairment in South Carolina with no restriction in regard to gender, race, age, and socioeconomic status. There are no exclusion or inclusion criteria which would exclude or preclude women or minorities from participating in this study. Women and minorities will be included in the research as they volunteer.

- **No children** will be included in this study; participants will be over 21 years of age. Children will not be included because childhood stroke requires a unique theoretical foundation guiding the design of rehabilitation therapy programs. Childhood stroke rehabilitation is beyond the scope of this study.

6.0 Number of Subjects

Study 1 DDP Intervention: Sample size was calculated based on FMA-UE data obtained from our previous work and the preliminary study described above[35, 37, 40] which, when the datasets were pooled, yielded a common standard deviation of 8 points. The study was powered to detect an 8-point difference in the pre- to post-training FMA-UE scores, a clinically meaningful change.[74] When comparing the two extreme groups (mild and moderate-severe impairment) with a Wilcoxon Mann Whitney test at a 5% significance level, a sample size of 20 individuals in each strata, for a total N=60, will yield 80% power to detect a minimum effect size of 1.00. Anticipating a 10% drop out rate evident in rehabilitation studies similar in duration/intensity to ours we will inflate the sample size to **N=66.**

Study 2 Focus Groups: Using Morse's guidelines,[75] 8 subjects per focus group will provide adequate data to reach saturation. Thus we will enroll a sample of **n=64** subjects for focus groups.

Rationale: Therapists and stroke survivors/caregivers represent distinct consumer groups. Each consumer group will provide different types of feedback based on their needs. Therefore, we will have **8 focus groups; 4 comprised of therapists from different practice settings and 4 comprised of survivors and caregivers**. To assure an equal representation from each consumer group we will enroll n=16 individuals with stroke, n=16 caregivers of individuals with stroke and n=32 stroke rehabilitation therapists to assure 8 subjects per focus group.

Study 3 Joint Angle Validation: 10 subjects with stroke and 10 neurologically healthy individuals will be enrolled.

Study 4: E-learning for At-Home Paretic Arm Use: This is a **proof of concept** study to ascertain the **feasibility** of stroke survivors ability to access and benefit of a newly developed Moodle e-learning module. Thus **n=3** subjects will be included.

7.0 Setting

Study 1 DDP Intervention:

- Research Laboratory: All outcome evaluations will be administered in the MUSC College of Health Professions Upper Extremity Function research laboratory.
- Subjects' Homes: Subjects will be provided with a laptop, Kinect, and/or X-box (depending on randomization) to take home. Subjects will play the computer games in their home environment. Dr. Woodbury's research team will phone each subject once per week. If a subject has a problem with the computer or software that cannot be resolved via phone, Dr. Woodbury or a member of her research team will visit the subject's home to fix it.

Study 2 Focus Groups: There will be a total of 8 focus groups.

- 4 will occur in the MUSC College of Health Professions Upper Extremity Function research laboratory,
- 4 will occur at Recovr headquarters in Clemson SC. Dr. Woodbury and her research team will oversee all focus groups.

Study 3 Joint Angle Validation

- Research Laboratory: The motion capture evaluation (Kinect and PhaseSpace) will be conducted in the MUSC College of Health Professions Upper Extremity Function research laboratory.

Study 4 E-learning

- Research Laboratory: The initial e-learning orientation and training session will occur in the MUSC College of Health Professions Upper Extremity Function research laboratory. In addition, all standardized assessments will be administered before and after the 4 week module in this laboratory.
- Subjects' Homes: Subjects will either use their personal device (phone, tablet or laptop) to access the e-learning Moodle course, or will use a laptop from the research laboratory (the same laptop used to play the DDP game) to access the Moodle course. Subjects will access the e-learning course from home.

8.0 Recruitment Methods

Study 1: DDP Intervention

Participants with stroke will be recruited from three sources:

- The Center for Rehabilitation Research in Neurological Conditions (CRRNC) stroke research recruitment database (approved MUSC IRB #15991) which currently contains ~250 persons with stroke who have signed informed consent and agreed to be contacted for research participation. Center affiliated investigators (such as the PI) can recruit subjects from this database.

- The COBRE Stroke Recovery Research Center (SRRC) stroke research recruitment registry called RESTORE (approved MUSC IRB #37803). The Registry currently contains the contact information for ~200 individuals with stroke who have provided consent to be contacted for potential participation in research studies. Importantly, the Center supports a dedicated project coordinator who enrolls 5-10 new participants into the registry per month and also supports information technology resources needed to maintain/update the Registry's infrastructure as needed.

- The South Carolina Young Stroke Survivors Support Group is supported in part by the MUSC College of Health Professions Department of Health Science and Research (the PI's home department) and the Roper-St. Francis Healthcare Network. It is a group of stroke survivors, caregivers and healthcare providers (therapists, nurses and research scientists) who provide emotional support, resource and educational support to persons whom have sustained a stroke at a young age. Approximately 30 survivors and their family/caregivers attend monthly in-person meetings in Charleston SC. Approximately 150 survivors are members of the group via Facebook. Information about the current study will be provided to this group for study recruitment.

- Flyers in stroke rehabilitation facilities and written advertisements in stroke recovery newsletters (e.g., Most stroke support groups have a newsletter).

Study 2: Focus Groups

Focus group participants will be recruited in the following ways:

- Individuals with stroke who participated in Study 1 (DDP intervention) will be offered opportunity to participate in the focus groups via a written recruitment letter.
- Caregivers of the individuals with stroke who participated in Study 1 (DDP intervention) will be offered opportunity to participate in the focus groups via a written recruitment letter.
- DDP is currently being used in several stroke rehabilitation facilities across South Carolina. A letter (to be developed once this project begins and will be approved in a future amendment to this project) will be sent to each of these facilities inviting their therapists to participate in the focus groups.

Study 3 Joint Angle Validation (a single evaluation visit of ~1 hour)

- Individuals with stroke who participated in Study 1 (DDP intervention) will be offered opportunity to participate in this study after their final parent study evaluation session.
- Caregivers of the individuals with stroke who participated in Study 1 (DDP intervention) will be offered opportunity to participate in this study. The project team will give caregivers information about this study during conversations with caregivers who typically accompany survivors to testing sessions in our research laboratory. In the past, we have found that caregivers are eager to participate in simple cross sectional evaluation sessions like this. A recent caregiver stated "*I like*

to do these evaluations too, it is exciting to be a part of things rather than just sit here and wait for (survivor's name) to finish!"

- Colleagues of the research team will be provided with broad information about this study during informal conversations and email correspondence. If a colleague expresses interest in participating, more detailed information will be provided verbally and/or in email.
- If the colleague would like to be considered for the study, he/she will schedule an in-person appointment with the PI or study therapist at the research laboratory. The potential participant will be read the inclusion/exclusion criteria for healthy participants (specified above). If he/she agrees that he/she meets those criteria, then informed consent will proceed as described below.

Study 4 E-learning

Three (**n=3**) participants who have completed the DDP intervention study described above (Study 1 above) will be recruited. Study team members will verbally inform subjects of the e-learning study during the final DDP intervention study visit.

9.0 Consent Process

Study 1: DDP Intervention

- Once a potential subject expresses interest in study participation, he/she will schedule an appointment to meet with the research team in the CHP upper extremity motor function research laboratory at a convenient time for the stroke survivor/caregiver's schedule. At that appointment, Dr. Woodbury (the PI) or an approved member of her research team will meet with the potential subject in a quiet, private room in the CHP Research Building. Several such rooms have been designated in this building for informed consent purposes. Dr. Woodbury or the research team member will read the informed consent form to the potential participant and his/her caregiver. To assure that the potential participant understands the study procedures, specifically the requirement for regular self-directed interaction with the computer game at home, Dr. Woodbury or the research team member will carefully explain these procedures and watch the potential participant and caregiver for signs of non-comprehension. The researcher will pause frequently to ask if there are any questions, and will answer those questions promptly. If needed, the potential subject and his/her caregiver will be shown a demonstration of the computer game (a demonstration console is located in Dr. Woodbury's research laboratory). The potential subject will be told that he/she can take as much time as needed to decide on study participation. If he/she seems unsure or hesitant, he/she will be encouraged to take the form home to re-read and call back with any questions. When ready, the subject will sign the informed consent form. It is possible that the stroke-related arm paresis may occur on his/her dominant hand which will make it impossible to use the dominant hand to sign the form. In that case, the subject will be encouraged to sign the form with his/her non-dominant hand.

Study 2: Focus Groups

- 4 focus groups will be held at MUSC. Once a potential subject expresses interest in study participation, he/she will schedule an appointment to meet with the research team in the CHP upper extremity motor function research laboratory at a convenient time for the potential participant's schedule. At that appointment, Dr. Woodbury (the PI) or an approved member of her research team will meet with the potential subject in a quiet, private room in the CHP Research Building. Several such rooms have been designated in this building for informed consent purposes. Dr. Woodbury or the research team member will read the informed consent form to the potential participant. Dr. Woodbury or the research team member will carefully explain the focus group procedures and watch the potential participant for signs of non-comprehension. The researcher will pause frequently to ask if there are any questions, and will answer those questions promptly. The potential subject will be told that he/she can take as much time

as needed to decide on study participation. If he/she seems unsure or hesitant, he/she will be encouraged to take the form home to re-read and call back with any questions. When ready, the subject will sign the informed consent form. It is possible that the stroke-related arm paresis may occur on his/her dominant hand which will make it impossible to use the dominant hand to sign the form. In that case, the subject will be encouraged to sign the form with his/her non-dominant hand.

- 4 focus groups will be held at Recovr headquarters in Clemson SC. The consent process for these participants will follow the same procedure as described in the previous paragraph, except that consent will be obtained at Recovr headquarters in Clemson SC rather than at MUSC. There are several small, quiet offices at Recovr which will be designated for informed consent.

Study 3 Joint Angle Validation

- The consent process for the subjects with stroke and neurologically healthy individuals will be the same as described above for Study 1. Note: this study will utilize its own informed consent because of the small sample size needed and that we do not expect all subjects enrolled in the parent study to participate in this smaller study.

- No children will be enrolled in this study, therefore there are no procedures for obtaining parental consent.

- No cognitively impaired adults will be enrolled in this study. As per the exclusion criteria, subjects' will be excluded if the Montreal Cognitive Assessment score <22 points.

Study 4: E-learning for At-Home Paretic Arm Use

- Once a subject completed the DDP intervention study described above (study 1), he/she will be told about this e-learning study by the study team. If he/she expresses interest, an initial session will be scheduled to obtain informed consent. The consent process will the same as per the procedures described above.

10.0 Study Design / Methods

Study 1: DDP Intervention

- Study Design: This is a prospective single-blind randomized trial with parallel arm design. N=66 individuals with post-stroke UE hemiparesis will be enrolled; 20 participants each per 3 UE impairment levels (mild, moderate, moderately-severe) as defined by the Fugl-Meyer Upper Extremity Assessment (FMA-UE) categories described in our previous publication.[36] A block randomization procedure will assure equal group size by assigning each patient to an impairment level based on the baseline FMA-UE. Within each stratum, a simple randomization procedure will be used to assign to treatment group (DDP vs. commercially available Kinect game).

- Research Procedures: All procedures described here are research procedures. There are no non-research procedures that will occur during study visits. All visits will be only for research purposes.

- Procedure: Subjects will travel to Dr. Woodbury's MUSC research laboratory 4 times for evaluation; pre-, mid-, post-treatment and 30 days post-treatment to test retention.

- Randomization to Treatment Groups: At the pre-treatment visit, after signing informed consent, the Fugl-Meyer Upper Extremity Assessment will be administered (see description below). Its summed score will be the basis for assignment to an impairment strata. Subjects within each stratum will be randomized to play DDP or a commercially available Kinect game, the *Kinect Target Shoot*. Both computer game interventions are described above in the section titled 3.0 Intervention to be Studied.

- To assure retention of enrolled subjects: During our preliminary study, we experienced unexpected post-randomization subject drop out. Each subject who dropped out reported that upon learning that he/she had not been randomized to the DDP group, he/she was no longer motivated to continue the study because he/she had hoped to play DDP. **Therefore, for this proposed study we will offer DDP to all subjects enrolled in the Kinect Target Shoot group**. We will not change the design of this prosed study, but instead offer the opportunity to play DDP for an additional 6 weeks after conclusion of the study, (i.e., after they have completed the 30 day retention testing) as a proactive way to address potential subject drop out. Data obtained from this additional DDP game-play will provide additional data for estimating effect sizes.

Schedule of Events								
	Pre-intervention visit	Intervention	Mid-intervention visit	Intervention	Immediately post-intervention visit	30 day follow up retention visit		For non-DDP players who cross over to DDP, immediately post-DDP intervention visit
Informed Consent	X	Either KTS or DDP for 9 sessions; 60 minutes per day, 3 days per week over 3 weeks Weekly phone calls from study therapist to participant		Either KTS or DDP for 9 sessions; 60 minutes per day, 3 days per week over 3 weeks Weekly phone calls from study therapist to participant			Non-DDP players will cross over and play DDP for 6 weeks (see section 10.0 of protocol for description) Weekly phone calls from study therapist to participant	
Screening Patient-reported: • stroke type • demographics • pain • orthopedic condition(s)	X							
Montreal Cognitive Assessment	X							
Orientation to computer game	X							
Fugl Meyer Assessment of the Upper Extremity	X		X		X	X		X
Wolf Motor Test	X		X		X	X		X
Kinematic Analysis	X		X		X	X		X
Stroke Impact Scale	X		X		X	X		X
Accelerometry	X		X		X	X		X

- Orientation to the computer game: At the pre-treatment visit, subjects will receive 30-60 minutes of training and for their assigned computer game, an instruction manual, laptop, and Kinect. Subjects in the Target Shooting group will also receive an X-box as is required for this game (but not for DDP). The study therapist will review the manual, demonstrate game set-up and play and provide instructions regarding study procedures. With therapist supervision, subjects will play the game while the caregiver operates the computer and provides coaching. Subjects will take the equipment home. The therapist will call the subject to verify successful at-home installation, and if needed, the therapist will travel to the subject's home to assist with in-home set up and provide further instruction. No further home visits will be provided unless the subject/caregiver encounters equipment or software problems that cannot be resolved via phone or email contact with study staff. Subjects will return the equipment at the final assessment session.

- Weekly Phone Calls: The therapist will phone each subject (both groups) weekly. During this phone call, the therapist will remind subjects of the importance of their participation in the activity, provide assistance with adjusting the game difficulty (see above), to document pain or fatigue (see below) and also will address concerns, questions, or technical difficulties.

- Dose: Dose will be matched across groups. All subjects will engage in 18 days (3 days per week over 6 weeks) of DDP or the commercially available game. All subjects will be instructed to play the game

for 60 minutes/day. It is likely that some subjects will choose to distribute this dose throughout a day. To assure matching does, custom software will be loaded onto the laptop that displays and records the duration of game play as it accumulates over a 24-hour period. Subjects will be instructed to "play the game until the timer shows that you have been playing for 60 minutes in a day."

- Rationale for the Dose: We chose this dose because it is similar to post-stroke arm rehabilitation programs having distributed practice schedules. For example, modified constraint therapy consists of 15 total hours of treatment; 30-minute sessions, 3 days/week for 10 weeks.[65] Similarly, UE functional task training consists of 18 total hours of treatment; 1 hour sessions, 3 days/week for 6 weeks.[66] and impairment oriented training consists of 20 total hours of treatment; 1 hour sessions, 5 days/week for 4 weeks.[67] Because some participants may not be able/ may not choose to complete 60 minutes each day, the intensity of training (averaged amount of time per day) will be added as a covariate to the primary analysis.

- Possible Fatigue and/or pain: The treatment program may induce fatigue and/or pain. Possible fatigue/pain is addressed in the following ways:

    - (1) Subjects will self-direct completion of the Borg Rating of Perceived Exertion (RPE)[76] each day. The RPE and instructions will be incorporated into the study's instruction manual which will be provided to subjects during the 1st baseline visit. Ratings of 12-14 on the Borg scale suggest that the activity requires moderate exertion. Because subjects will self-direct their own treatment we expect that they will self-monitor and take breaks as needed and therefore we do not expect ratings to reach or exceed this level. However, we will provide clear instructions that if an RPE rating is above 14, the subject should rest and contact the study therapist.
    - (2) The study therapist will phone each participant weekly to inquire about and document client self-reported pain, especially pain in the paretic shoulder on a 0-10 ordinal pain scale.[77] If a client reports pain ≥5 (moderate), he/she will be instructed to cease the study intervention for the day. If the subject reports that pain has been moderate or severe (≥5) for several consecutive days, the subject will be counseled to stop the study and to contact his/her physician.

Study 2: Focus Groups

Aim 3: Determine the treatment validity of the DDP report as a measure of impairment and response

- Rationale: A review of the literature and therapy practice guidelines did not provide a template to guide a clinically useful performance report, thus motivating this aim. The purpose is to answer two questions: what information about the session does a therapist need, and what information does the patient/caregiver need? From a therapists' perspective, useful output will guide documentation and/or treatment planning. From a survivors' perspective, useful output will increase knowledge of their own impairments to empower future interactions with the medical team (e.g., ask informed questions, co-plan subsequent treatments). Informal feedback from therapists, patients and caregivers that we have received on the current report suggests a need to optimize this report.

- **Focus Groups:** To develop an informative DDP performance report we will elicit the perspectives and opinions of the consumer group by[78] conducting 8 focus groups; 4 each at the (1) Medical University of South Carolina, Charleston, SC and (2) Recovr headquarters in the Greenville SC area. Each group will last ~2 hrs.

    - Procedure: During the first 30 minutes, we will provide participants with an overview of DDP background/development. During the subsequent 90 minutes, we will show de-identified videos of stroke patients playing DDP. The Focus Group leader (Dr. Woodbury) will guide

a discussion about (1) what elements of the player's performance would a clinician select as most relevant for documenting patient status/progress in his/her practice setting, and (2) what elements would a patient/caregiver select as most informative to him/her.

- The group discussion will be guided with a Focus Group Guide[79] to address the core elements of the performance report's utility,[80] i.e., ease of interpretability, format, meaning to the therapist, meaning to the patient/caregiver). Dr. Jillian Harvey, who is an experienced qualitative researcher, will oversee development of the Focus Group Guide.
- *Audio recording:* The focus group will be audio recorded. The rationale for audio recordings is to develop a transcript of the discussion that will be used to establish critical discussion themes. These themes will then guide the design of the performance report's elements. Woodbury will lead the groups and a designated project member will monitor an audio recorder. Immediately after each session, we will upload the digital files into a dedicated secure file on the MUSC network. Audio files will be transcribed by a professional transcription service.
- *Field Notes:* A project member will take detailed Field Notes to record the sequence of speakers, notable consumer reactions (facial expressions, etc.) and any other non-verbal activities.

Study 3 Joint Angle Validation (a single evaluation visit of ~1 hour)

Aim: To validate a new method of measuring shoulder and elbow range of motion.

- Rationale: We have written new software codes to analyze Microsoft Kinect arm motion tracking. We anticipate that the new calculations of joint ranges of motion are more accurate than our previous measurements, but have no evidence to support this hypothesis.
- Study Design: A single cross sectional evaluation session that will be ~1 hour duration.
- Procedure: 10 neurologically healthy individuals and 10 individuals with stroke will attend a single evaluation session in our motion capture laboratory. Each subject will be seated on a backless stool in a standardized starting position. Subjects will be instructed to "reach as fast as you can" to touch virtual targets on a computer screen. The subject will view an arm avatar on the computer screen which is controlled by a Kinect motion sensor (as in the Duck Duck Punch computer game described above). Subjects will reach to hit the virtual targets by moving his/her physical arm. The targets will be positioned at a location of ~80% of arm's length and located in each of 9 locations: at, below and above the horizon at midline and at 30 degree angles to the right and left of midline. The purpose of this 9 target grid is to measure shoulder and elbow angles throughout the reaching workspace in order to understand how our joint angle calculations with the Kinect may be affected by arm configuration relative to the Kinect sensor. Moreover, all of these target locations will afford maximum shoulder flexion and elbow extension[68] and thus elicit maximum and minimum joint angle measures. The Microsoft Kinect will record arm location at the same time that kinematic data are recorded with a 10-camera PhaseSpace motion analysis system. The PhaseSpace data will be analyzed as described in the Aim 1 procedures above. The Kinect joint angles will be calculated using our new computer software codes, then Kinect measurements will be compared to the same joint angle measurements made with the PhaseSpace system.
- Data Analysis: The concurrent validity of the Kinect-based measures compared to the PhaseSpace measures will be assessed with an Intra Class Correlation Coefficient (ICC). Acceptable measures will be defined as similar within a 10 degree measurement error.

Study 4: E-learning for At-Home Paretic Arm Use

Aim 4: Test the feasibility of an e-learning module to elicit patient self-directed paretic arm use in their home

Rationale: Results from recently concluded large stroke rehabilitation clinical trials clearly indicate a disparity between paretic arm use during (1) therapy vs. (2) at home or in the community. That is, patients

safely accomplish hundreds of paretic arm movement repetitions during a structured therapy session. Yet, they fail to translate motor skills from clinic to home. As documented by wrist-worn activity monitors, patients rarely move the paretic arm during non-structured (non therapist initiated) real-world home/community activities. Reasons for this disparity include patients' self-reported lack of knowledge regarding optimal ways to care for him/herself after therapy has ended. It is likely that the current therapy model of in-clinic therapist-guided arm movement practice inhibits patients' development of self-management skills by reinforcing reliance on the therapist's guidance for arm use which renders patients' unskilled in self-directed skill implementation. In efforts to address this problem, we created an online learning module within MUSC's Moodle e-learning platform for stroke survivors designed to bridge the gap between the clinic and home. The purposes of this e-learning module are to (1) provide information about stroke motor recovery to elicit cognitive learning for self-management and (2) coach stroke survivors during at-home paretic arm use via therapist-patient teleconferences to elicit psychomotor learning for self-management.

Study Design: This is a **proof of concept** study to ascertain the **feasibility** of stroke survivors ability to access and benefit from the Moodle e-learning module.

Subjects: Three (3) stroke survivors who have completed the DDP study described above will be recruited to test the e-learning module.

Procedure: After obtaining informed consent, the 3 subjects will begin the study together as a group.

- Subjects will attend an in-person e-learning orientation/training session. The learning module's purpose and objectives will be reviewed. Subjects will be shown how to access the e-learning module (e.g., sign on, click through the course menu, access a lesson, contribute to a discussion, sign into a tele-conference), and then practice these tasks under the in-person supervision of study staff who can answer questions and provide extra training as needed. The e-learning module is offered on Moodle, the MUSC e-learning platform. Subjects will use their own device (laptop, tablet or phone) for the course. However, if they do not have a device, a laboratory laptop computer (dedicated for laboratory research studies with its configuration already approved by MUSC OCIO and CHP IT) will be made available for participants to take home for the duration of the study. MUSC students and faculty easily and routinely access Moodle learning modules from personal devices, thus we do not expect that participants will have difficulty accessing the course once they become familiar with the environment.
- After this training session, subjects will be tested for paretic arm motor ability (Fugl-Meyer Upper Extremity Assessment), self-reported difficulties with at-home arm use (Stroke Impact Scale), and self-efficacy with home arm use (Self Efficacy Scale).
- Subjects will then participate in the course for 4 weeks at home. Each week the course will offer (1) a lesson such as a video, reading, or Panopto-recorded lecture from a research team member (or other stroke rehabilitation expert), (2) an asynchronous discussion about the lesson via the course Discussion Board, and (3) a video teleconference meeting between the 3 subjects and the study's occupational therapist. The overall idea is that the lesson will address reasons why at-home paretic arm use is important (e.g., to facilitate long term neural plasticity), facilitate the subjects to set arm use goals for themselves, receive tips/pointers from the therapist for implementing home arm use, and engage in peer support with other survivors who are also seeking to use their paretic arm more.
- At the end of the 4 week course, subjects will return to MUSC for a final testing session where the measures of paretic arm movement ability, self-reported at home arm use, and self efficacy will be re-administered.

11.0 Specimen Collection and Banking

- No specimens will be collected or banked.

12.0 Data Management

Study 1: DDP Intervention

- Sample size was calculated based on FMA-UE data obtained from our previous work and the preliminary study described above[35, 37, 40] which, when the datasets were pooled, yielded a common standard deviation of 8 points. The study was powered to detect an 8-point difference in the pre- to post-training FMA-UE scores, a clinically meaningful change.[74] When comparing the two extreme groups (mild and moderate-severe impairment) with a Wilcoxon Mann Whitney test at a 5% significance level, a sample size of 20 individuals in each strata, for a total N=60, will yield 80% power to detect a minimum effect size of 1.00. Anticipating a 10% drop out rate evident in rehabilitation studies similar in duration/intensity to ours we will inflate the sample size to **N=66.**
- Hypothesis: We hypothesize that DDP will improve arm motor skills more than the commercially available game. The rationale for this hypothesis is that the difficulty of DDP game play can be adjusted according to the patient's level of ability in order to elicit arm movement practice at the "just-right" level of difficulty, neither too difficult nor too easy, to maximize post-stroke motor skill relearning and skill reacquisition.
- Missing Data: Since each patient will be observed over a 3-month period, it is possible that the patient will miss a visit and/or drop out. If a patient misses a testing session we will make all attempts to reschedule. If the patient drops out an intent-to-treat analysis will be applied and the missing data will be treated as missing at random (MAR). If missing occurs, multiple imputation methods will be used for data analysis (PROC MI and PROC MIANALYZE, in SAS version 9.3). The biostatisticians will oversee this process.
- Dependent Variables: Five dependent variables will measure arm motor skills; (1) reduction of arm motor impairment as measured by the FMA-UE, (2) improved arm motor function as measured by the WMFT, (3) improved voluntary shoulder and (4) elbow ranges of motion, and (5) reduced trunk (T-10) movement compensation as measured by kinematic analyses.
- Independent Variables: The independent variables are Treatment and Time. The between subjects factor "Treatment" has 2 levels (DDP vs. Kinect Target Shoot) with 3 impairment levels nested within each level (mild, moderate, severe). The within subjects factor "Time" has 4 levels; Pre, Mid, Post and Retention.
- Data Analysis of Primary Outcome Variables:
    - Two, two-way mixed model ANOVAs will be used to assess the main effects of Treatment on the primary outcome measures (FMA-UE, WMFT and kinematic variables). The intensity of training (averaged number of minutes of game play per day) will be a covariate. Significance for all comparisons will be alpha = 0.05.
    - Segmented Regression Modeling: For each DDP subject, we will estimate specific thresholds that mark the number of movement repetitions associated with a change in the Interjoint Coordination (IJC) treatment response using segmented regression analyses. To understand the relevance of this analysis, consider the pilot data presented in **Figure 8** above. As shown, this subject seemed to have a negative treatment response in the first week of the DDP program. That is, she exhibited more elbow flexion than elbow extension when reaching forward to hit DDP targets as evidenced by a downward slope in the curve. Then, on day 5 she exhibited dramatic gains in elbow extension as evidenced by the upward slope of the curve. The shift from a downward to an upward slope is marked by the day 5 data point which is like a joint between the segments of the curve. The segmented regression model will capture this phenomenon. In this analysis we will essentially fit two linear (or polynomial) regression models that meet at a common value called the joint-point (threshold). The threshold will be defined as the number of movement repetitions at which this joint-point occurs. In addition, we will calculate the average rate at which each individual improves elbow extension (slope of the line) after reaching the threshold.

- Growth mixture modeling (GMM): We will follow the segmented regression modeling with GMM, which offers a robust statistical procedure to "uncover" heterogeneous treatment response patterns. While conventional statistical modeling assumes a single mean value and variance, GMM allows several mean values around which subgroups vary thereby showing how different people recover in different ways. The GMM will calculate "growth classes" of subject groups who show similar patterns of change in IJC. Our a-priori hypothesis that subjects in each impairment strata (mild, moderate, moderate-severe) will show distinct patterns of recovery, i.e., we expect 3 classes of recovery. We will test whether there is one overall pattern of recovery that describes the entire sample (1-class), whether there are two patterns of recovery within the sample (2-classes) or whether there are three patterns of recovery in the sample (3-classes). The models are not nested (a 1-class model is not a subset of the 2-class model) because different individuals will make up each class and so we will define the best fitting model as the one having the lowest Bayesian Information Criteria (BIC) and an entropy value closest to 1.0.
- Relating Dose to Response: After separating the sample into classes, we will average the threshold movement repetition values for each class (identified in the segmented analysis) and calculate a 95% confidence interval for of repetition values for each class. In addition, we will calculate the average rate at which each class improves IJC (slope of the line) after reaching the threshold. This will allow us to determine the relationship between dose and response for each group.

- Data Analysis of Secondary Outcome Variables: We will utilize ANOVAs to test the effect of Treatment on the average SIS-hand item rating and the average SIS-recovery scores. In addition, we will analyze the accelerometry data using a within-group repeated measures analysis to compare subjects' first week AAR to final week AAR in order to determine if the treatment program elicited gains in subjects' use of the paretic arm relative to the non-paretic arm. **The secondary outcome data have an important purpose**. At the conclusion of this study we anticipate a subsequent Phase III SBIR proposal of a larger, multi-site RCT that will enable clear decisions regarding the clinical utility and commercialization of DDP to therapists and stroke survivors. Our plan is to power that study on a measure of "real-world" paretic arm use. We reason that successful commercialization of DDP requires a clear understanding of how DDP elicits a motor recovery process that enables stroke survivors to integrate his/her paretic arm within the context of a meaningful daily activities. Therefore, obtaining SIS and accelerometry data in the present study will inform our decisions about which tool is the best measure of real-world use, and also inform future sample size calculations.

Study 2: Focus Groups

- *Sample Size:* Using Morse's guidelines,[75] 8 subjects per focus group will provide adequate data to reach saturation. Thus we will enroll a sample of **n=64** subjects for focus groups. Rationale: Therapists and stroke survivors/caregivers represent distinct consumer groups. Each consumer group will provide different types of feedback based on their needs. Therefore, we will have **8 focus groups; 4 comprised of therapists from different practice settings and 4 comprised of survivors and caregivers**. To assure an equal representation from each consumer group we will enroll n=16 individuals with stroke, n=16 caregivers of individuals with stroke and n=32 stroke rehabilitation therapists to assure 8 subjects per focus group.
- *Coding of Data:* Once checked, the transcripts will be imported into QSR International's NVIVO 8 software for coding. The coding process involves reviewing text, line by line, to identify embedded concepts in order to develop a coding framework hierarchy. Drs. Harvey and Woodbury will be responsible for coding. They will develop the initial coding framework then meet with the research team to review and discuss. The team will recommend revisions as necessary.
- *Analysis:* Data will be analyzed using the constant, comparative method commonly used in qualitative analysis.[82] All data will be subject to the coding framework; if an existing code is found to be representative, it will be coded accordingly. If existing codes are not representative, a new

code will be added, and then the data recoded. As data are coded, the investigators will review the text related to individual codes to define patterns among themes. We will use the themes to identify aspects of treatment validity that can provide the basis for modifications of the performance report, review potential modifications, and finalize the reports.

- *Efforts to ensure the trustworthiness of data:* We will follow guidelines for ensuring the trustworthiness and quality of conclusions drawn from qualitative data.[83] Definitions of codes, revisions to the coding framework, and project member debriefings will provide continuing documentation to ensure that project findings are objective and can be replicated.
- *Multiple Iterations:* We will obtain consensus on the report's content and design using a Delphi method because it gauges usefulness of opinions based on repeated feedback.[84] Procedure: Working at each step with a graphic designer (who will be employed by the company Recovr), we will conduct the Delphi via a website for participant convenience (the same participants as for the focus groups). The prototype report, as initially designed based on focus group feedback, will be posted at an MUSC supported (secure) site. Participants will be asked to rate their endorsement of each section on a 4-point scale (strongly dislike, dislike, endorse, strongly endorse) and provide a brief rationale. Using Green's criterion, sections that obtain a rating of 3 (endorse) or higher by 70% of the participants or a median of ≥3.25 will be retained from the 1st round and not presented in the next round.[86] Sections that do not reach this criterion will be re-designed based on comments provided, and re-presented to panelists in the next round. Our goal is to meet consensus on all sections. If we cannot meet consensus, we end the rounds once panelists report an average of <15% change in their responses over the repeated rounds[87] and select the sections with the highest median ratings.
- The information from the focus groups + Delphi method will then be incorporated into a finalized report and incorporated into DDP.

Study 4: E-learning for At-Home Paretic Arm Use

- Study Data: This is a proof of concept feasibility study. Prior to, and immediately following the 4 week e-learning course, data will be collected to document subjects' (1) paretic arm movement ability via the Fugl Meyer Upper Extremity Assessment; (2) self-reported difficulties using the paretic arm via the Stroke Impact Scale; and (3) self efficacy via the Self Efficacy Scale. In addition, subjects' comments on the feasibility of accessing the course will be documented.
- Analysis: No statistical analysis will be done. Instead, only descriptive data will be presented so as to provide an indication of the feasibility of an e-learning module to elicit self management skills. These data will provide pilot data for a future, properly powered clinical trial of the e-learning self-management course.

Describe the steps that will be taken to secure the data to maintain confidentiality

- The above data will be collected by study staff all of whom will have documentation of human subjects training.

- All data will be de-identified prior to storage on the MUSC network. That is, PHI will separated from the data prior to its storing. After signing informed consent, subjects will be assigned a study specific identification code that will not contain PHI. This de-identified code will be used to identify the participant throughout the study.

- There will be one hard-copy file that will link the study code to the participant's name. The only people having access to this file will be the PI and study coordinator. The hard-copy file will be stored in a locked cabinet in the study coordinator's office.

- All electronic records will be stored in password protected files on the MUSC network with the highest level of security available at the time.

- Identifiable data will not leave MUSC, documents with identifiers (e.g., ICF, enrollment log) will be kept at MUSC and stored in a locked cabinet in the study coordinator's office. Only de-identified data will be shared with Recovr for the purposes of scientific presentations, manuscripts, and continued commercialization of DDP.

13.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

- *What will be monitored:* Study subjects will be monitored for fatigue and pain.
- *How frequently:* Subjects will be monitored weekly during phone calls from the study therapist to the participant. As per procedures described above, each subject will keep a record of fatigue using the Borg Rating of Perceived Exertion scale in his/her study manual. He/she will be instructed to record this value daily throughout the study. The study therapist will phone each participant weekly to inquire about and document these fatigue ratings. In addition the study therapist will document client self-reported pain on a 0-10 ordinal pain scale. Recommendations will be made based on the input received.
- Ratings of 12-14 on the Borg scale suggest that the activity requires moderate exertion. Because subjects will self-direct their own treatment we expect that they will self-monitor and take breaks as needed and therefore we do not expect ratings to reach or exceed this level. However, we will provide clear instructions that if an RPE rating is above 14, the subject should rest.
- If a client reports pain ≥5 (moderate) on the pain scale, he/she will be instructed to cease the study intervention for the day. If the subject reports that pain has been moderate or severe (≥5) for several consecutive days, the subject will be counseled to stop the study and to contact his/her physician.
- Any and all adverse events will be reported to the MUSC IRB as per regulations.
- *Who will monitor:* Subjects will be monitored by research therapist who will phone each subject weekly. The research therapist will report on each participant to the study PI weekly, or daily if the therapist judges that the subject is having pain or fatigue. The PI and research therapists are licensed occupational therapists with extensive experience providing rehabilitation programs to persons with stroke.
- *Endpoint:* For subjects initially randomized to DDP, the study endpoint will be the 30 day follow up retention test. For subjects initially randomized to KTS, the study endpoint will be the immediately post-DDP play visit which will occur 6 weeks after the 30 day follow up (or approximately 4 months from study enrollment). Subjects will be able to terminate the evaluation sessions and/or rehabilitation protocol at their request at any time without prejudice.

14.0 Withdrawal of Subjects

- Subject Withdrawal:

  As participation in this study is voluntary, the subject has the right to withdraw from the study at any time for any reason without prejudice to his/her future stroke rehabilitation care. For the subject who withdraws consent, the date and reason for withdrawal will be documented. Subject data will be included in the analyses up to the date of withdrawal and no further data will be collected.

- Subject removal from the study:

  The PI may stop study therapy if there is a safety concern (e.g., excessive pain/fatigue), if the subject fails to attend evaluation sessions or adhere to study procedures. Subject data will be included in the analyses up to the date of withdrawal and no further data will be collected.

15.0 Risks to Subjects

Repetitive arm motions may cause fatigue or pain: Participation in any movement activity program may cause fatigue and/or muscle soreness. As per the procedures described the study therapist will phone each participant weekly to monitor fatigue and pain.

Randomization: The subjects will be assigned to a treatment group by chance. The treatment group they receive may prove to be less effective than the other activity group.

Loss of confidentiality: Dr. Woodbury's team will take appropriate steps to protect subject data. However there is a slight risk that information could be revealed inappropriately or accidentally. All hard-copy information with the subjects name on it will be stored in a locked cabinet in a locked office in a secure building at the MUSC (77 President Street, Charleston, SC). All electronic information will be stored in a secured database on the firewall protected MUSC network. No PHI will be transmitted outside of MUSC, stored on portable electronic devices, shared or sold at any time. All of the data from the test results will be de-identified before it is stored in a research database

16.0 Potential Benefits to Subjects or Others

- Although we anticipate that subjects will benefit from this study by gaining arm/hand motor function, there is no guarantee of benefit. However others may benefit from our increased understanding of how computer games may be used to elicit repetitive practice of arm movement for stroke recovery. Future therapies may be improved upon by this knowledge

17.0 Sharing of Results with Subjects

- Subjects may submit a written request for their arm movement assessment results. This information will be provided to them in hard copy form.

18.0 Drugs or Devices

- DDP has FDA 510(k) clearance (K151446). The clearance notification letter from the FDA indicates that the software is cleared "for use with the Microsoft Kinect motion tracking system that is indicated to support physical rehabilitation of adults in the clinic and at home via performance of therapist-assigned reach exercises for the upper extremities. Patient assessment, exercise guidance, and approval by the medical professional are required prior to use."

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