Effectiveness of Functional Strength Training in Virtual Reality Games for Improving Arm Function in Children with Cerebral Palsy – A Pilot Sequential Multiple Assignment Randomized Trial (SMART) Design

A. Research Questions

Cerebral palsy (CP) is the leading cause of childhood physical disabilities.[1-2] About 1 in 303 school-aged children in the U.S. is diagnosed with CP and about half of these children have impaired arm function, or difficulty in reaching, grasping, and manipulating objects.[3-4] Animal and humans studies have shown that improving arm function requires hundreds of repetitions per day of a challenging functional task to lead to structural neurological change.[5-6] The required number of repetitions is very challenging to achieve in a single therapeutic session.[7] Thus, therapeutic exercises should not only be performed in the clinical setting, but should be sustained in the home environment between clinical visits to maximize the effectiveness. Unfortunately, many factors affect parents and children's compliance in performing therapeutic exercises at home, including forgetfulness, lack of motivation, boredom, and lack of immediate feedback.[8-11] Moreover, the heterogeneity nature of children with CP makes the effectiveness of home interventions varies.[1,2,12] Tailored home interventions that enable continuity-of-care are clearly needed. These interventions must provide sufficient challenge, motivate the child to perform, enable seamless integration of clinical objectives, and provide instant feedback to enhance the child's skill learning.[13-14] One such intervention is virtual reality (VR)!

Virtual reality (VR) has been shown to be a viable tool for creating an interactive, motivating environment for intensive training for children.[15-16] VR applications use interactive simulations that respond to a user's movement such that a child can interact with a virtual environment while performing functional activities.[15-16] VR can also provide immediate visual and auditory feedback and can easily adjust task difficulty to provide sufficient challenge for a child. Researchers have recently investigated the efficacy of VR in helping children with CP improve arm function.[17-23] In single case studies, including our own prior work, large effect sizes have been shown to improve arm function in children with CP.[17,23] A recent meta-analysis done by our group also confirmed the effect of VR and showed a home-based and engineering-built VR may provide a large effect size than a clinic- or laboratory-based and commercially available VR system.[24]

On the other hand, for adult-based rehabilitation, a form of functional strength training (FST: strengthening while performing functional activities) has been shown to improve reaching movements, arm function, and even quality of life in individuals with stroke.[25-27] However, the effect of using FST in the upper extremity in children with CP has not been explored. The closest study has been the examination of FST on lower extremity and gait performance in children with CP.[28-29]

Since children with CP have been known to have large heterogeneity in the responses of receiving interventions, the fixed intervention approach study design may not meet the need.[30-32] There is growing interest and need for research on how to adapt and re-adapt intervention to maximize clinical benefits. Our overall goal is to use sequential multiple assignment randomized trial (SMART)[30-32] to develop valid, high-quality adaptive interventions using VR and FST to improve arm function in children with CP (see Figure 1). The treatment adapted here is by augmenting or switching to the other intervention. Before conducting a "full-scale" SMART design, it is necessary to conduct a **pilot** SMART project to fine tune the study design and evaluate its feasibility and acceptability.[31] Through this first preliminary study, a foundation can be laid for further research by testing the hypothesis that the use of VR and FST would result in an increased rate of upper extremity motor progress in children with CP. This will form the basis for a subsequent study submission to federal (i.e., NIH, NIDILRR) and private (e.g., Cerebral Palsy Foundation) funding agencies for extramural grants to fund a "full-scale" SMART project.

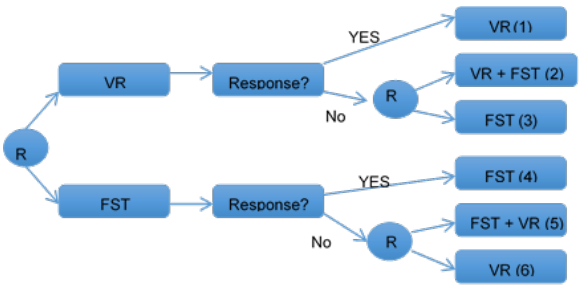

Figure 1. Research design. R: randomization; VR: virtual reality; FST: Functional Strengthening Training

Four adaptive interventions (ATS) are considered in this pilot SMART trial: **ATS1** (subgroup 1+2 in Figure 1)- First treat with VR only for 6 weeks. Then, if the child does not respond to initial VR, augment treatment by initiating a combination of FST and VR for another 6 weeks; otherwise, if the child responds to initial VR, maintain on VR alone for another 6 weeks; **ATS2** (subgroup 1+3)– First with VR, later switch to FST for children with CP who do not respond well to initial VR; **ATS3** (subgroup 4+5) – First with FST, later augment with a combination of VR and FST for children with CP who do not respond well to initial FST; and **ATS4** (subgroup 4+6) – First with FST, later switch to VR for children with CP who do not respond well to initial FST.

The **research questions** asked in this pilot SMART are:

1. What is the preliminary direction of the intervention effectiveness?
    a. Is to begin adaptive interventions with VR better than with FST?
    b. Which of the 4 embedded adaptive interventions (ATS) lead to the greatest improvement in arm function in children with CP?
2. Are the proposed adaptive interventions acceptable to participants and feasible to the research team?

B. Innovation

1. *An evidence-based innovative approach to examine the individualized intervention to meet the practical need in clinics*. We use SMART design to systematically examine the ATS to improve arm function in children with CP, which reflects the real-world intervention approach: for non-responders, therapists switch to an alternative intervention method. This project can provide the preliminary evidence for clinical practice.
2. *Tailored-made intervention at home with a low-cost platform to provide accurate and precise evaluation of reaching movements.* Our newly designed Super Pop VR^{TM} platform provides a home-based evaluation metrics and can accurately measure the reaching kinematics.[33-35] Moreover, home-based intervention model can decrease the burden for both children and their parents since they will be in their home, this intervention can be arranged to fit the family's daily routine, to save the family travel time and the associated costs, and potentially increase social-interaction for the children with their family members.

C. Research Methods

C.1. Team and Previous Studies from the Research Team

Team: The multidisciplinary research team has an excellent combination of expertise and experience necessary to successfully complete the project. PI Chen is a pediatric physical therapist with expertise in pediatric rehabilitation (e.g. VR, robot, strengthening) in children with CP. Dr. Howard is an electrical engineer with extensive experience designing and utilizing VR and assistive technologies to engage children in therapy. Drs. Weissman and Hallman-Cooper are the pediatric neurologists in Children's Healthcare of Atlanta (CHOA) and faculty members in Emory University. They have a designated CP clinic and around half of their patients in other clinics are also children with CP. Dr. Ruiyan Luo, a biostatistician, has deeply involved in study design and will provide further consultation for data analysis and interpretation.

Preliminary Studies: The research team has been involved in research that develop and evaluating the effectiveness of a VR system on arm function in children with CP[23,33-36] as well as to design a vision-based algorithms to autonomously extract upper-arm kinematic metrics during interaction with virtual environment.[37-41] Preliminary clinical work also has demonstrated poor motor control in the reaching patterns of children with CP and additional studies have shown improvement on arm control that occurs through practice in children with CP.[42-44]

C.2. Approach

Study Design: A SMART design will be used.[30-32] The children will be firstly randomized to either VR alone or FST alone intervention for 6 weeks. Then, they will be evaluated at the end of the 6th week to be determined whether they are responders or non-responders. For those who respond to the first assigned intervention, the children will continue receiving the same intervention for another 6 weeks. For those who are non-responders, they will then be randomly assigned to either a combination intervention (VR + FST) or a switch to the other intervention (Figure 1).

Participants: Since this is a pilot SMART study, twenty children with spastic hemiplegia type CP will be recruited from the CHOA CP Clinic, local school system, local pediatric physical therapy clinics, Parent-to-Parent of Georgia, and other parent support groups. Inclusion criteria are: 1) children are between ages 6-12 years; 2) diagnosed with spastic hemiplegia; 3) have a Manual ability classification system (MACs) level I-III; 4) able to sit with trunk supported; 5) are able to reach forward for more than half of their arm length; 6) are able to complete a cognitive task (Kauffman Briefed Intelligence Test- 2nd edition) with a minimum cognitive age of 5 years; 7) are able to see video screen (with or without corrected vision); and 8) their primary caregiver is willing to follow the desired intervention 'dosing' and all evaluation measurements. Children will be excluded if 1) they have received surgery or botulinum toxin type A injection in the training arm within the preceding 4 months or are scheduled to receive it during the planned study period, or 2) if they have a severe attention deficit or uncontrolled epilepsy which may possibly be triggered by the light or sound of the video games.

Intervention.

Interventions:

1. VR intervention – In this project, we focus on using our developed VR gaming platform called Super Pop VR™, a VR system that can be individualized to the movement capabilities of the child (Figure 2). Super Pop VR™ combines interactive game play for encouraging user movement with an objective and quantifiable kinematic algorithm that analyzes the user's upper-arm movements in real-time. It consists of the Microsoft Kinect camera, a laptop, software, and TV screen. The research team will loan the system to the family. While engaged with the game, the child is immersed in a virtual world where virtual objects appear on the screen surrounding the child. Children are asked to move their arms to 'pop' as many virtual objects as possible in a certain amount of time. The VR intervention is designed to train children with CP to move their affected arm in overhead, outward, and across midline directions, which are not the typical pattern children with CP perform. The bubble size, location, speed can be easily manipulated in the game to provide sufficient challenge to the children.

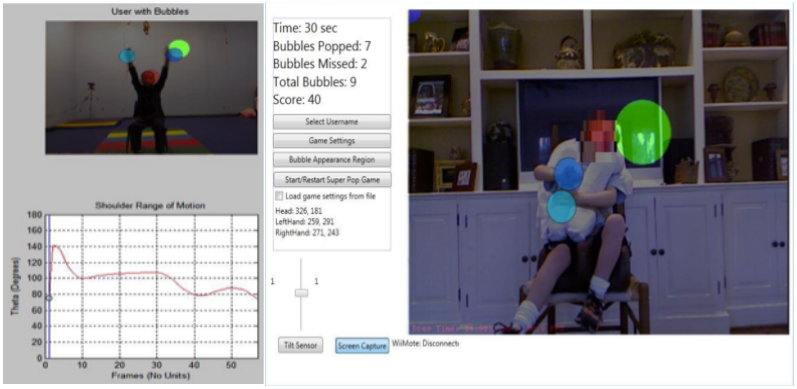

Figure 2. *Super Pop VR™* - a virtual reality game for upper-extremity movement therapy

2. Functional Strength Training (FST) – FST involves repetitive progressive resistance exercise during goal-directed functional activity with the children focus on the activity being performed. Children will be offered a pamphlet containing suggested functional arm exercises and these exercises are designed to move their affected arm in overhead, outward, and across midline directions. Each exercise will be embedded in a game-like activity (see Figure 3 as an example). Children will start with no resistance and gradually add on resistance using elastic bands or weight cuffs.

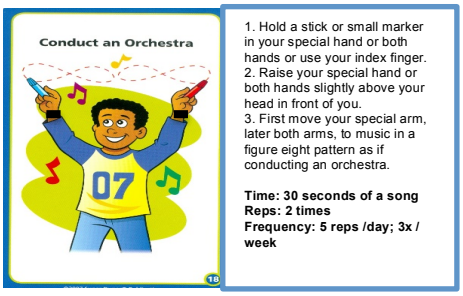

Figure 3. An example of functional strength training (FST)

3. *Combination of VR and FST intervention* – If the children do not respond well to their first assigned intervention and they are randomly assigned to receive the combination therapy, they will receive the combination of both interventions. Children will be required to wear weight cuffs around their wrist when playing the VR games. The intensity and frequency of the intervention will be the same as VR alone or FST alone.

Procedure:

All data will be collected at the children's home. After the telephone screening, the research team will schedule their first visit with the family. The children's primary caregivers will complete IRB-approved consent forms and verbal or written assent will be also obtained from the children. Randomization to first intervention will take place prior to the first meeting. At the first meeting, the pre-intervention evaluation and an instruction session on how to conduct assigned intervention will be introduced. If needed, the research team will visit the family within one week to make sure the primary caregiver is comfortable of conducting the intervention. The family can also set up multiple online observation sessions with the research team using FaceTime or Skype to have as much technical support as they want.

After the introduction session, the children will then start to perform the home intervention for 60 minutes per day, 3 days per week for 6 weeks. At the beginning of each week during the intervention, a researcher will conduct a home visit to review the child's performance, encourage the family to adhere to the designated dosing, progress the child's training for the next week, and back up the stored play data. The primary caregiver will be asked to record in a log about 1) games played, 2) duration of playing, 3) perceived game difficulty level, and 4) comments regarding the their feeling about the activities their child play or any comments related to the child's feeling (e.g., enjoy the game). In order to remind the family to perform the designated intervention, all primary caregivers will also receive an email or text reminder on the morning of their exercise day. The email/text will provide the link to watch the short video clips to remind them the exercise content they should perform for that day.

After receiving 6 weeks of intervention, the children will be evaluated to determine whether they are responders or non-responders. For those who are responders, they will continue receiving the same dosage and type of intervention. That is, children who are assigned to VR will continue receiving VR for the next 6 weeks; children who are assigned to FST will continue receiving FST for the next 6 weeks. For those who are

non-responders, children will be randomly assigned to augmenting the other intervention or switching to the other intervention. That is, for children who are assigned to augmenting the other intervention (i.e. the combination group), they will receive the combination of FST and VR for the next 6 weeks. For children who are assigned to switch to the other intervention, children who are assigned to VR in the first 6 weeks will receive FST for the next 6 weeks; whereas children who are assigned to FST in the first 6 weeks will receive VR for the next 6 weeks. Similar instruction, visit, and email reminder will be conducted as what they receive in the first 6 weeks.

Measures:

Since this is Pilot SMART to examine the two research questions proposed earlier. The measures will be addressed based on the research question.

- **Research question 1: What is the preliminary direction of the intervention effectiveness: a. Is to begin adaptive interventions with VR better than with FST? b. Which of the 4 ATS lead to the greatest improvement in arm function in children with CP?**

All children will be evaluated prior to first intervention (pre-test 1), immediately after the 6-week intervention (post-test 1), 2 weeks after the first intervention is done (pre-test 2), and immediately after the second 6-week intervention (post-test 2). The changes between pre-test 1 and post-test 1 will be used to determine whether the child is a responder or a non-responder.

1. Primary outcome measures: including reaching kinematics, standardized fine motor assessment tool, and daily use of affected hand. A physical therapist who is blinded to the research purpose and the child's intervention status will conduct the assessment.

Reaching kinematics will be assessed while the child is interacting with Super Pop VR^{TM}, wherein virtual bubbles are projected onto the TV in randomly dispersed locations, using the Kinect system. Three testing bubbles will be tested in the location where children need to reach about arm length overhead at 180, 135, and 90 degrees of shoulder abduction, with instructions for children to reach in two conditions: 1) as fast as possible, and 2) as accurate as possible. Children will also assess the reaching kinematics while playing the real-life functional activity by inserting an envelope into a mailbox slip located in neutral, outward 45 and inward 45 using the Kinect system. All children will be seated in an adjustable chair with a testing table in front of them at waist height with trunk support. Data will be collected for a minimum of 6 reaches for each direction of virtual and real-life tasks. Position data from the Kinect will be converted into 3-dimensional coordinate data and kinematic variables (movement time, trajectory straightness, speed, smoothness) will be computed. We have successfully validated the kinematic measures using Kinect system with well-accepted motion analysis system.[40,45-46]

Standardized fine motor assessment tool. The fine motor domain of the Peabody Developmental Motor Scales-2nd edition (PDMS-2) will be used.

Daily use of affected hand will be evaluated using Revised Pediatric Motor Activity Log (R-PMAL), which is filled by primary caregivers about how often and how well their children use the affected arm in daily activities.

2. Secondary outcome measures:

Muscle strength of shoulder flexion, extension, abductor, adduction, external rotation, and international rotation, elbow flexion and extension, and wrist flexion and extension will be measured using hand-held dynamometer prior and after intervention. Range of motion of shoulder flexion, extension, abduction, adduction, external rotation, and internal rotation, elbow flexion and extension, and wrist flexion and extension will be measured using a standardized goniometer. Spasticity of shoulder flexion, extension, abduction, adduction, external rotation, and internal rotation, elbow flexion and extension, and wrist flexion and extension will also be measured using the Modified Ashworth Scale. It contains a scale of 0 to 4 with 0 as no spasticity to 4 as rigid in flexion or extension. Two-point discrimination and joint proprioception on both arms will be evaluated to represent the children's sensation. Children's motivation and compliance to the intervention will also be evaluated using the daily activity training log. The primary caregiver will be asked to keep an activity training log to record their child's training activity, including the daily training and the total time when the child takes part in the training. The total duration of performing the VR or conventional program will be calculated as the measure of compliance. We will ask caregivers to record the reasons for not completing the daily training.

3. Determination of responders and non-responders:

A responder is defined as the change between pre-test 1 and post-test 1 need to exceed clinically significant effect of at least two reaching kinematic variables and one functional assessment tools (i.e., PDMS-2 or R-PMAL), similar to the literature.[47] The clinically significant effect of reaching kinematics measured by Super Pop VR^{TM} are 0.34 s for movement time, 0.20 meter for straightness, 0.879 m/sec for speed, and 0.3 for

smoothness.[35,45-46] The clinically significant effect of functional assessment tools are 4.935 for PDMS-2, 0.67 for "how often" in R-PMAL, and 0.66 for "how well" in R-PMAL.[48-49]

- **Research question 2: Are the proposed adaptive interventions acceptable to participants and feasible to the research team?**

In order to evaluate the acceptability to participants, a survey and an exit interview will be conducted at the end of completion. Children and their primary caregiver will be asked how satisfied they feel about the ATS they receive, any barriers they experience during the intervention and how to improve. The survey and exit interview will also be conducted by the blinded therapist.

To evaluate the feasibility to the research team, the duration spent to educate the family and to visit the family will be recorded. Also, number of reminders or phone calls sent by the research team will also be recorded. A survey and exit interview will also be conducted to further understand the barriers of conducting each adaptive intervention.

Data Analysis

To compare the effect of VR and FST, the main effect of the first stage intervention, we will compare the mean of each primary outcome measure for all children receiving VR (subgroups 1, 2, 3 on Figure 1) with that for all children receiving FST (subgroups 4, 5, 6). To identify which of the four embedded adaptive interventions leads to the greatest improvement in outcome measures, we will compare the means of the adaptive intervention groups (subgroups 1 and 2, 1 and 3, 4 and 5, 4 and 6). As the responding children are sampled only once, the non-responding children are sampled twice and then under-representing the outcomes from non-responding children, we will assigns weights 4 for non-responders and weights 2 for responders. Then we will get the weighted mean of each of the four adaptive interventions and then compare.

The results from the survey will be summarized using descriptive analyses. The qualitative method will be used to examine the theme ideas from the exit interviews. All the statistics will be analyzed using SAS.

D. Anticipated Results and Impact

By achieving the goals of this project, we seek to improve health outcomes for children with upper-extremity motor limitations by enabling individualized therapy through the combination of VR and/or FST. Based on prior work by the PIs in assistive technologies and clinical studies with children with cerebral palsy, we believe we have laid the foundation for bridging the gap between engineering research and real-world clinical application. Outcomes are expected in the development of approaches that ultimately allow therapists to provide evidence-based adaptive interventions to enhance their arm function and to conduct a full-scale SMART project to determine the optimal adaptive interventions. As part of our research objectives, our goal is to have 3-4 conference papers and 2-3 journal publications compiled based on the technology development efforts and results derived from the study. The PIs have experience in and will continue to disseminate research in the communities of interest, including International Journal of Virtual Reality, Physical Therapy, Developmental Neurorehabilitation, Developmental Medicine & Child Neurology and the Journal of Human-Computer Interaction.

E. Timeline

The project high-level milestones are illustrated below. There are many associative lower-level activities that will take place to meet these deadlines.

Task Activity	1st Quarter		2nd Quarter		3rd Quarter		4th Quarter	
VR & FST preparation								
Participants recruitment								
VR & FST Intervention								
Study Analyses								
Evaluation/Grant Preparation								

F. Plan for Extramural Funding

This research will examine the preliminary effect of using a SMART design to examine the effectiveness of VR and FST on arm function in children with CP. This study will lay the groundwork for securing additional funding through NIH, NIDILRR, both of whom will be pursued for conducting a full-scale SMART design (NIH: R01 or R15, October, 2016; NIDILRR: early 2017). We will also pursue extramural funding from the Cerebral Palsy Foundation as this project also meets their research priorities.

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