Effectiveness of Virtual Reality Exercises in STroke *Rehabilitation* (EVREST): Rationale, Design, and Protocol of a Pilot Randomized Clinical Trial Assessing the Wii Gaming System

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Background Evidence suggests that increasing intensity of rehabilitation results in better motor recovery. Limited evidence is available on the effectiveness of an interactive virtual reality gaming system for stroke rehabilitation. EVREST was designed to evaluate feasibility, safety and efficacy of using the Nintendo Wii gaming virtual reality (VRWii) technology to improve arm recovery in stroke patients.

Methods Pilot randomized study comparing, VRWii versus recreational therapy (RT) in patients receiving standard rehabilitation within six months of stroke with a motor deficit of ≥ 3 on the Chedoke-McMaster Scale (arm). In this study we expect to randomize 20 patients. All participants (age 18–85) will receive customary rehabilitative treatment consist of a standardized protocol (eight sessions, 60 min each, over a two-week period).

Outcome measures The primary feasibility outcome is the total time receiving the intervention. The primary safety outcome is the proportion of patients experiencing intervention-related adverse events during the study period. Efficacy, a secondary outcome measure, will be measured by the Wolf Motor Function Test, Box and Block Test, and Stroke Impact Scale at the four-week follow-up visit. From November, 2008 to September, 2009 21 patients were randomized to VRWii or RT. Mean age, 61 (range 41–83) years. Mean time from stroke onset 25 (range 10–56) days.

Conclusions EVREST is the first randomized parallel controlled trial assessing the feasibility, safety, and efficacy of virtual reality using Wii gaming technology in stroke rehabilitation. The results of this study will serve as the basis for a larger multicentre trial. *ClinicalTrials.gov* registration# NTC692523

Key words: cortex reorganization, feasibility, outcome research, randomized clinical trial, rehabilitation, safety, stroke, virtual reality, Wii gaming system

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Dr Robert Teasell and Dr. Leonardo G. Cohen both equally contributed to the manuscript and project to qualify as the senior investigators.

Background

Stroke devastates patients and their families. Up to 85% of stroke survivors immediately experience hemiparesis, resulting in impairment of an upper extremity associated with diminished health-related quality of life (1).

Traditional methods for rehabilitation post stroke are demanding, tedious, resource-intense, and provide a limited benefit for patients with a motor dysfunction (2). Recent approaches involving repetitive training of the paretic upper extremity on task-oriented activities have been shown as beneficial, particularly for stroke survivors who are able to retain some ability to actively extend the fingers and wrist of their paretic upper extremity (3, 4). Virtual reality is computer technology that simulates real-life learning and allows for increased intensity of training while providing augmented three-dimensional and direct sensorial (visual, sensory and auditory) feedback. This is a novel technology that allows users to interact with a computer-generated scenario (a virtual

world) making corrections while performing a task. There has been limited research involving the inclusion of virtual reality gaming systems in neuro-rehabilitation and there is an identified need for rigorous randomized controlled trials to establish the feasibility, safety, efficacy, and value of virtual reality in the stroke populations (5).

We hypothesized that virtual reality using Wii gaming technology is feasible, safe and potentially efficacious in enhancing motor function of the upper extremity required for activities of daily living compared to recreational therapy among stroke patients receiving standard rehabilitation as implemented in Canada.

Study design

The ongoing EVREST (**E**ffectiveness of **V**irtual **R**eality **E**xercises in **ST**roke Rehabilitation) trial is the first randomized, single blinded study with two parallel groups to systematically compare the influence of virtual reality using Nintendo Wii © gaming technology (VRWii), versus recreational therapy (RT) on motor function of the upper extremity among patients who experienced a first stroke within 10–60 days prior to enrollment. In Canada, rehabilitation is standard of care in the first three to six months after stroke. EVREST is a pilot trial designed to evaluate feasibility and safety of the widely available Wii gaming system versus recreational therapy for patients receiving usual care (standard rehabilitation).

Participants

Participants 18–85 years within six months from the first-time ischemic or hemorrhagic stroke were eligible for the study. This time window was chosen as it's when the opportunity for facilitating motor recovery is expected to be optimal (2, 3). All participants had a clinically defined acute stroke confirmed by neuroimaging (CT or MRI) or written medical reports and met a level of function of the upper extremity derived from the Chedoke-McMaster scale (6) stage greater than three, either in the arm or hand at time of enrollment. Inclusion and exclusion criteria are summarized in Table 1.

Baseline measures

Patient characteristics were collected at baseline including demographics (age, gender), handedness, comorbid conditions, stroke characteristics including location, type, subtype (according to TOAST), severity (NIHSS), and disability at baseline based on the modified Rankin scale (mRS), and Barthel Index (BI) for activities of daily living. Baseline motor function was assessed using the Wolf Motor Function Test (7) and the Box and Block Test (8), and baseline quality of life was assessed using the Stroke Impact Scale (9) (Fig. 1) Assessors were trained and accredited in the use of the scales.

Table 1 Inclusion and Exclusion criteria

Inclusion Criteria (all):
- Signed written informed consent prior to entry into the study
- Males or females, aged over 18 and younger than 85
- Evidence of stroke confirmed by CT head (ischemic or hemorrhagic)
- Time: Onset of symptoms within 6 months prior to randomization
- Measurable Chedoke-McMaster scale stage greater than 3 on the hand or arm
- Functional independence prior to present stroke (baseline mRS = 0–1)
- Patient is alert, medically stable according to the treating physician and able to follow simple verbal commands

Exclusion Criteria:
- Acute stroke onset more than 6 months prior to study entry
- Patient is unable to follow verbal commands or has global aphasia
- Severe illness with life expectancy less than 3 months (i.e.: cancer, endocarditis, metastasis with an occult primary malignancy).
- Uncontrolled hypertension according to the treating physician
- Unstable angina or recent myocardial infarction (within the last 3 months), current NY Heart Association Class III (marked limitation of physical activity; although patients are comfortable at rest, less-than-ordinary activity leads to fatigue, dyspnea, palpitations, or angina3) or IV (symptomatic at rest; symptoms of CHF are present at rest; discomfort increases with any physical activity) or symptomatic ventricular tachyarrhythmias, as per medical history (a baseline ECG will not be required.)
- Any history of seizure (previous or during the stroke index), except for febrile seizures of childhood.
- Participation in another clinical trial involving rehabilitation (recreational therapy, occupational therapy, physiotherapy) or an investigational drug.
- Patient is unwilling or unable to comply with the protocol or can not/will not cooperate fully with the investigator or study personnel.
- Any medical condition that might confound the interpretation of results or put the patient at risk (amputation of one extremity).

Study interventions

Description of Wii gaming technology

Nintendo Wii® introduced a new style of virtual reality (2005) by using a wireless controller that interacts with the player through a motion detection system and its avatar representation in the video. The controllers use embedded acceleration sensors that can respond to changes in direction, speed, and acceleration to enable participant's wrist, arm, and hand movements to interact with the games. A sensor, mounted on top of a TV, captures and reproduces on the screen the movement from the controller as performed by the participants. As Wii is computer-assisted, big sweeping movements in the games are unnecessary. The feedback provided by the TV screen generates a positive reinforcement, thus facilitating training and task improvement. The simple graphics and possibility to reduce speed make it usable for patients with cognitive impairment. Further details are described online. (http://www.nintendo.com/wii/what).

Description of RT

Recreational therapy sessions included leisure activities such as playing cards, stamping a seal while playing bingo and/or

Study Procedure		Screening/ Baseline	Training	Intervention Sessions		Post-Intervention Follow-Up	4-Week Follow-Up
	Visit:	1	2	3-9	10	11	12
	Elapsed Time:	0	<------------ 0 - 14 days ---------->			14 days	6 weeks
	Visit Window, days		<---------- * ---------->			+3	±3
Informed consent		×					
Medical history and patient characteristics prior to stroke		×					
Assessment of qualifying stroke NIHSS Stroke subtype (TOAST classification)		× ×					
Modified Rankin Scale Score		×					
Barthel Index		×				×	×
Randomization		×					
Stroke Impact Scale		×				×	×
Wolf Motor Function Test Score		×				×	×
Box and Block Test Score		×				×	×
Administer questions about physical symptoms before and after interventional sessions			×	×	×		
Specific games played and time			×	×	×		
Borg Perceived Exertion Scale			×	×	×		
Wii Test Score at End of Session			×		×		
*These 8 sessions can be scheduled in a flexible manner as long as all 8 sessions are completed within the 2 week period, and no more than 2 sessions are completed on any one day. If 2 sessions are completed on one day, they must be undertaken at least 5 hours apart.					NIHSS = National Institutes of Health Stroke Scale TOAST = Trial of Org 10172 in Acute Stroke Treatment		

Fig. 1 Schedule of trial-related assessments

playing 'Jenga'. Patients were instructed to remain in a sitting position and primarily use their more affected arm/hand in these activities. Adherence to standard rehabilitation and to the study tasks were monitored with a timer. RT was used as a control group for the following reasons:
● to allow a fair comparison between the time spent in rehabilitation activities between groups
● lack of evidence that Wii gaming system is standard rehabilitation therapy.

Study procedures

Randomization
Participants were randomly allocated in a 1:1 ratio to the two study groups. The randomization schedule was computer generated using a basic, random number generator.

Allocation
All participants, admitted at Toronto Rehabilitation Institute, received the standard rehabilitation therapy for stroke, which accounts for an average of two hours of physiotherapy and occupational therapy per day upon tolerance.

Sessions
Patients randomized to VRWii technology received an intensive program consisting of eight Wii sessions of 60 min each over a 14 day period. The eight sessions were scheduled in a

flexible manner as long as all sessions were completed within the two-week period, with sessions separated by minimum eight hours. A 60 min training session was delivered to introduce the interventions. The software used in EVREST was sports (i.e. Wii Sports) and 'Cooking Mamma' packages.

Blinding of caregivers and outcomes measures assessment

The study coordinator and patients participating in this study were not blinded to the intervention group. To limit knowledge of Wii gaming technology, and to ensure other caregivers and support staff were not aware of subject allocation (which may introduce bias) as far as possible, all study interventions were conducted by dedicated trial staff out of sight of ward staff. Trial staff and subjects were instructed not to divulge the intervention allocation to caregivers or other ward staff. Interventions were not recorded in the medical records or videotaped.

Contamination
At final follow-up, the blinded assessor was asked to select (forced choice) to which group they thought the patient had been allocated. This process allowed us to assess whether protocols to blind the assessor to group were effective.

Follow-up visit

Follow-up data was collected four weeks (+/− three days) after the final study intervention session.

All baseline, post-treatment and 4 week follow-up assessments were performed by a trained outcome assessor who was not involved in the administration of study interventions, blinded to patient randomization.

Outcome measures

Primary outcome measures

The co-primary end-points of the present study relate to feasibility and safety. Time tolerance and adaptation for Wii have not been formally tested in stroke patients. Therefore, the *primary feasibility outcome* is defined as the total time receiving the intervention.

The *primary safety outcome* is assessed by the proportion of patients experiencing intervention-related adverse events, or any serious adverse event (SAE) during the study period. A SAE was defined as any untoward medical occurrence, whether or not considered to be causally related to the study intervention that resulted in death, was life-threatening, required in-patient hospitalization, or prolonged hospitalization, resulted in persistent or significant disability or incapacity.

Secondary outcome measures

Efficacy was a secondary outcome in EVREST. *Efficacy* was measured as an improvement in motor function determined by total time elapsed to complete a shorter version of Wolf Motor Function Test (WMFT). Other efficacy end-points include a 4-point improvement on the Box & Block Test (BBT), and overall improvement in quality of life measured by the Stroke Impact Scale (SIS) in the four-week follow-up visit.

Statistical analysis

Baseline characteristics will be summarized with suitable descriptive statistics. The primary endpoint is feasibility. Thus the proportion of prescribed therapy time will be estimated for each group and summarized with confidence intervals. Differences between the groups on feasibility are not of primary interest, nor are differences expected and so statistical testing is not a primary goal. The study was not powered to detect clinically significant differences in the secondary (efficacy) endpoints. Nevertheless, adjusted regression analyses will be performed to provide preliminary data for treatment effects and variability.

Study organization and data management

The study was completed at Toronto Rehabilitation Institute, which receives referrals for in-patient stroke rehabilitation from 4 acute care facilities in Toronto.

Administrative activities, data management, research co-ordination and statistical analyses were conducted at the Applied Health Research Centre (AHRC) at St. Michael's Hospital, University of Toronto. Operational procedures, guidelines for the implementation of both arms of the study, and the informed consent were approved by the ethics review boards at St. Michael's Hospital and Toronto Rehabilitation Institute. Written informed consent was obtained at Toronto Rehabilitation Institute prior to enrollment.

Recruitment

The study was launched November 2008. September 2009, 21 patients were randomized to EVREST; mean age was 61 (range 41–83) years. Mean time from stroke onset to enrolment was 25 days (range 10–56 days).

Discussion

EVREST represents the first randomized, controlled study to systematically test virtual reality technology using the Wii gaming system as neurorehabilitation therapy in patients with first stroke within two- months prior to enrolment. EVREST was designed to evaluate safety and feasibility of virtual reality using the publicly available Wii gaming technology in stroke rehabilitation.

Interestingly, the design of randomized trials in stroke rehabilitation constitutes a scientific challenge due to several factors, including: impossibility of double-blinding interventions, target population and patient selection, limitations in defining a definitively comparable control group, all of which limit sample sizes, thus affecting the interpretation of the results. The recent publication of well-design randomized trials using treadmill (10), repetitive bilateral arm training (11), or constraint-induced movement (4) provided new insight by adding other strategies to the traditional approach in stroke rehabilitation.

Despite these recent advances, EVREST represents the first randomized trial of virtual reality using the Wii gaming system in neurehabilitation after stroke.

Motor improvement post stroke may occur as a result of spontaneous recovery; learning and practice due to reorganization in the brain. Studies suggest this process is significantly enhanced with task-specific and intensive training (12) Virtual reality has emerged as the new paradigm in computer-assisted technology to allow for increased intensity of training while providing augmented sensory feedback. More than just playing or training, the implementation of virtual reality technology may gear use-dependent neuroplastic changes post-stroke. Studies using functional MRI showed that functional recovery correlates most closely with reorganization in ipsilesional peri-infarct and related contralateral cortical areas (13). Studies using transcranial magnetic stimulation have shown that recovery of perilesional inhibition and intracortical disinhibition of the motor cortex contralesional to the infarction may

play an important role in brain reorganization (14, 15). Recent evidence suggest the role of 'mirror neurons', which discharge during the execution or observation of various hand-directed actions performed by other individuals enhance and explain motor recovery (16, 17). Under similar principles, action observation in association with physical training can also enhance the effects of motor training after stroke (18); similar mechanisms may be implicated in virtual reality using Wii gaming technology.

EVREST is a novel trial evaluating the role of virtual reality using Wii gaming technology neurorehabilitation after stroke. The results of secondary end-points will serve to calculate the necessary sample size for a potential larger multicentre trial. Our study constitutes the initial step in the understanding of the potential benefit of interactive rehabilitation using Wii gaming technology post-stroke with potential implication for daily patient care.

Author's contribution statement

We declare that we have participated in the (conception, design, analysis, interpretation of the results, drafting the manuscript and made a critical revision of the manuscript).

Dr. Kevin Thorpe (biostatistician), Dr. Gustavo Saposnik and Judith Hall had full access to the data.

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EVREST Steering Committee:

The Steering Committee is composed of the principal investigator of EVREST (Dr. Gustavo Saposnik), principal investigator at Toronto Rehabilitation (Dr. Mark Bayley), the Research Manager (Judith Hall) and Director (Muhammad Mamdani) at AHRC who made all decisions concerning the implementation and conduction of the study.

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