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The VIRTUE study: Can virtual reality games help people with cognitive impairment following a stroke to regain the ability to perform daily activities?

Submission date
29/09/2019

Recruitment status
No longer recruiting

Registration date
03/10/2019

Overall study status
Completed

Last Edited
29/03/2023

Condition category
Nervous System Diseases

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol
Strokes commonly affect the way we understand, organise and store information as well as interact with our environment- often referred to as ‘cognitive impairment’. These 'cognitive impairments' after a stroke might affect the patient’s ability to concentrate, remember information, plan or solve problems they routinely face during their day-today activities, notice or recognise things, or navigate their home and surroundings. Fortunately, some of this cognitive impairment improves with intensive guided practice, and there is some evidence that suggests that therapy using virtual reality based computer programs can speed up this improvement.
We are funded by the 'Innovate UK' to develop a virtual reality based post-stroke cognitive rehabilitation program called 'VIRTUE'. The program contains different tasks and scenarios resembling normal activities of daily living that the patient would perform during their regular therapy sessions. Each task will be graded with different levels of complexity to suit the patient’s abilities and rate of recovery. The plan is to deliver additional therapy sessions to the participants by a semi-trained therapist along with their regular therapy sessions. VIRTUE trial designed is to test the feasibility, optimum dosing and acceptability of VIRTUE. We are planning to recruit 60 eligible participants in the first three weeks after stroke. The trail has two arms. In the active treatment arm, participants will receive VIRTUE sessions at a different dose and duration, along with their regular therapy sessions.
Also, in the control arm participants will receive a sham virtual reality based treatment for two weeks along with their usual therapy sessions. Participants from both these groups will be tested their cognitive function before the start of their treatment, after completion of VIRTUE /sham VIRTUE treatment and also at three months. Any adverse event from the treatment will be monitored continuously during these three months.

Background and study aims
A stroke is when the blood supply to part of the brain is cut off, either because a blood clot blocks a blood vessel or the blood vessel bursts. The lack of oxygen and nutrients to the brain cells can cause damage to the brain. Depending on which part of the brain is affected, a person

might have problems with a certain function, such as thinking, speech or movement. Cognitive impairment means a problem with the way people understand, organise and store information and how they interact with their environment. This is a common problem after someone has had a stroke and often means they cannot look after themselves initially, but it can be improved with training and practice.
This trial aims to investigate whether a virtual reality program, where a person can interact with a computer-generated environment to practice everyday activities, can help them regain the ability to perform these activities more quickly than if they only did the usual occupational therapy.

Who can participate?
Adults who have had a stroke within the past 3 weeks and have cognitive impairment.

What does the study involve?
The participants will be randomly allocated to one of two groups. Both groups will receive the usual therapy for someone who has cognitive impairment following a stroke. One group will use the virtual reality program every day for 2 weeks. In the program, the participants will be asked to perform an activity, such as making a cup of tea. The activity will get more difficult, for example the first time the person makes a cup of tea in the virtual kitchen, all the items needed will be visible, but later on, the items will be in different cupboards. The other group will use a different virtual reality program every day for 2 weeks. This program is not designed to help improve the person's ability to do daily living activities.
Both groups will be assessed before the start of the treatment, after the end of the treatment at 2 weeks after the start of the treatment, and at 3 months after the start of the treatment.

What are the possible benefits and risks of participating?
One of the possible benefits that could occur from taking part in this study is the increased recovery rate of cognitive abilities. The results will be used to further develop the use of Virtual Reality (VR) technologies for cognitive rehabilitation.
There is a potential risk of experiencing a side effect of VR called cyber-sickness, which present similar symptoms to motion sickness. If this does occur, the participant can ask for the headset to be removed immediately.

Where is the study run from?
Countess of Chester NHS Foundation Trust (UK)

When is the study starting and how long is it expected to run for?

Who is funding the study?
Innovate UK

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
265538

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
IRAS 265538

Study information

Scientific Title
VIRTUE: VIRTUal reality based cognitive rehabilitation immediately after a strokE: a double-blind phase 2b pilot randomised controlled trial to identify the optimum dosing, acceptability of VR-based treatment and test the feasibility.

Acronym
VIRTUE

Study objectives
Stroke is a leading cause of death and disability worldwide (Feigin, VL 2014), costing 5.5% of the total healthcare cost in the UK (Saka 2009). Although sensory-motor impairments are easily identifiable neurological deficits after a stroke, more than two-thirds of patients in the acute stage (Nys GM, 2005) and 57.7% in 3-6 months (Dong Y, 2012) suffer from post-stroke cognitive impairments (PSCI) , which are hard to detect without proper screening (Burton L, 2015) and are strongly associated with: a reduced ability to undertake activities of daily living (ADL) (Claesson L, 2005); increased caregiver strain (Claesson L, 2005); higher cost of post-stroke care (Claesson L, 2005) due to inability to return to work or participate in hobbies and social activities (Miller EL, 2010); higher rate of institutionalisation (Pasquini M, 2007) and most importantly, a higher mortality (Pasquini M, 2007) as compared to those without PSCI. Also, PSCI places a huge overall burden on the healthcare system (Feigin, VL 2014).

Recovery from a stroke often depends on cortical reorganisation resulting from neuroplasticity. Neuroplasticity is highly dependent on a targeted intensive therapy delivered by a multi-disciplinary team (Dobkin BH, 2004) within the first few weeks after a stroke, which provides a critical time window within which most significant neuroplastic changes take place within the undamaged part of the brain (Lang CE, 2009). However, stroke sufferers spend more than 80% of their daytime in non-therapeutic activities, of which 28% was spent sitting down (Bernhardt J, 2004, Huijben-Schoenmakers M, 2009). In the UK, the National Institute of Clinical Excellence (NICE) recommended at least 45 minutes of rehabilitation therapy delivered by a multidisciplinary team for at least five days a week (NICE CG162, 2013). This recommendation, often not fulfilled in most of the stroke units across the UK due to the cost pressure, lack of availability as well as lack of understanding behind this recommendation by trained therapists (Clarke DJ, 2018).

Currently, rehabilitation for cognitive impairments following a stroke predominantly follows a varying combination of remedial therapy and compensation for underlying impairments utilising practice and repetition of tasks or actions guided by therapists (NICE CG 162). Reviews of outcomes for this approach for cognitive impairments following a stroke are mixed, suggesting a need for further research and improved interventions (Hoffmann T, 2010). Despite the method of intervention, it is clear that the dose of intervention plays a vital role in the improvement in cognitive function in these patients (Quaney BM, 2009; Walker CM, 2004).

Personalised medicine and technological advances offer new potential avenues for treatment. For instance, computerised task training is effective in improving cognitive impairments post-stroke, possibly because it allows for increased dosage and training which can also be tailored to the needs of the patient (Westerberg H, 2007). Virtual reality (VR) utilises interactive simulations generated using computer hardware and software. It presents the user with a virtual environment, often similar to the real world, which they can engage and interact with (Weiss PL, 2014). VR for rehabilitation is a relatively recent development, but it has already been utilised for clinical interventions to treat phobias, posttraumatic stress disorder, and body image disorders (Freeman D, 2018, Jiandani N, 2014; Raghav K, 2016). Use of technology in older people is increasing, and in the future, virtual reality is likely to become more commonplace in clinical rehabilitation settings (Burridge, JH, 2010: Bohil CJ, 2011). VR rehabilitation offers features, such as goaloriented tasks and frequent repetitions that have been shown to play a crucial role in neurological rehabilitation (Langhorne P, 2011; Veerbeek JM, 2014). Computerised approaches to rehabilitation allow for practice of functional tasks at a higher dosage than traditional therapies which require the presence of an occupational therapist or physiotherapist (Demain S, 2013; Fung V, 2012; Kwakkel G, 2004). Another advantage of VR is that it permits clinicians to practise or trial tasks that would be unsafe to perform in the real world, e.g., crossing the street or using potentially dangerous appliances (Laver, 2017). VR can offer an enriched experience compared to traditional therapies; animal research shows that training in enriched environments results in improved cognitive performance in tasks such as problem-solving compared to the conventional approach (Risedal A, 2002). This approach utilises the concept of ‘immersion’ - the extent to which the user believes that they are in the virtual environment – as well as the flexibility to tailor the task and environment to maximise desired outcomes or benefits for the user. VR tasks are rated as more interesting and enjoyable by users than computer task alternatives, which encourages more practice and repetition that could underlie clinical benefits (Lewis GN, 2012). Therefore, VR rehabilitation for stroke could provide an enriched and tailored environment for patients to practise and master new skills at an increased dosage to existing interventions. In addition to these clinical benefits, VR’s ability to deliver an increased dose of taskspecific training without requiring intensive increases in trained staff time will provide economic benefits and open up treatments to more patients (Laver KE, 2017).

A modest amount of research suggests positive outcomes for VR based therapies in post-stroke upper limb motor impairments, which have been extensively reviewed (Laver KE, 2017), but few

studies have considered outcomes for cognitive impairments. Two open labelled randomised controlled trials (with small sample size) have compared the efficacy of VR based cognitive rehabilitation programmes with the conventional treatment in the subacute (Kim BR, 2011) and in the chronic phase (Faria AL, 2016) after a stroke. Both these trials demonstrated a significant improvement in some of the cognitive domains, such as visual-spatial construction, recall and digit span, in the VR group as compared to the controls. Although these preliminary findings were encouraging, more research is needed to understand the recruitment rate, participants' and staffs' acceptability, adherence to the treatment, and optimum dosing as well as the efficacy of the VR based cognitive rehabilitation, in the most crucial phase (Lang CE, 2009) of recovery following a stroke before conducting a multi-centre phase III trial for this treatment.
Based on these principles, we have developed a collaborative clinical project between the Department of Computer Science, University of Chester; Countess of Chester Hospital NHS Foundation Trust and Cadscan Ltd., called VIRTUE - Virtual Reality for Cognitive Stroke Rehabilitation, which has been funded by Innovate UK (Project grant number: 104545) in September 2018. As a part of this project, we have developed virtual reality-based serious games in the following day to day tasks: grooming, dressing, various kitchen activities, shopping and recreational activities (e.g. shopping in a supermarket, buying a cup of coffee or ordering a meal in a restaurant). The games are graded at different levels of complexity and the level of difficulty increases in every level either by adding an additional task (such as while preparing a cup of tea the ingredients will be visible on the kitchen top at the beginning, but at the higher level patient has to collect some or all the ingredients from their usual storage spaces). Visual and verbal clues provided by an 'Avatar' built within these games become less and less at a higher level. These games are developed following the same treatment principle used by a trained occupational therapist in the UK; however, the VR treatment sessions will be provided by a therapy assistant or by a carer in addition to the usual care provided by a trained occupational therapist.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Approved 11/09/2019, North West - Haydock Research Ethics Committee (3rd Floor - Barlow House, 4 Minshull Street, Manchester M1 3DZ; +44 (0)207 104 8012; nrescommittee.northwest-haydock@nhs.net), ref: 19/NW/0419
2. Approved 23/09/2019, HRA & HCRW), ref: 19/NW/0419

Study design
Randomised sham-intervention controlled trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Cognitive impairment following a stroke

Interventions
Stage 1: Screening: Adult patients (over the age of 18 years) admitted with a stroke (ischaemic or haemorrhagic: diagnosis confirmed by a stroke physician) will be screened consecutively using

the pre-specified inclusion/exclusion criteria. Recruitment is required within 3 weeks of index stroke. Screening log: Recruitment and reasons for exclusion or declining (if offered by the patient) will be documented using a detailed screening log.

Stage 2: Recruitment: After reviewing the inclusion and exclusion criteria, all eligible patients will be invited by a GCP-trained healthcare professional to take part in this trial. They/their next of kin will receive the written study information and will be allowed to ask questions before obtaining written consent. The consent will be obtained by a GCP-trained experienced stroke research nurse either from the potential participants or from participants' next of kin if the patient lacks capacity. Also, if the patient is unable to write due to his/her weakness, independent witness consent will be obtained.
We will recruit up to 60 patients exhibiting post-stroke cognitive impairment (PSCI) established by a score of less than 26 out of 30 on the Montreal Cognitive Assessment (MoCA) over a 1-year period. The baseline assessment will be obtained by a trained research nurse/therapy assistant before the randomisation procedure.

Stage 3: Baseline assessment, which will be obtained by face-to-face interview

Stage 4: Randomisation: Following the completion of the baseline assessment, patients will be randomised and will be stratified based on baseline MoCA score in two groups (<15 and 15-25) on a 3:1 allocation basis to receive either VR plus usual care or sham VR plus usual care.

Stage 5: Intervention:
Treatment group 1 (VIRTUE therapy plus usual care):
40 patients with PSCI in the VR group will receive daily therapy sessions using the VIRTUE application. During these sessions, the VIRTUE therapy will be presented through a head-mounted visual display (HTC Vive).
Design of dose finding of VR based cognitive rehabilitation therapy:
Despite routinely conducting phase I and phase II dose optimisation trials in pharmaceutical research, optimum dose-finding trials are rarely performed in any rehabilitation research. Recently, Colucci et al. published their methodological paper on dose finding in upper limb therapy after a stroke (Colucci, 2017), and this section of VIRTUE follows the same principles and a 3 + 3 rule-based, dose-escalation design will be adapted for this intervention.

Control group (sham VR therapy plus usual care):
Participants will receive a sham VR treatment for 2 weeks along with their usual care. The control group is included to assess the feasibility of using sham VR as a blinding method for the phase III trial.

Stage 6: Post-treatment cognitive assessment using Cognitive Assessment of Minnesota and MoCA will be assessed by an independent assessor unaware of the treatment allocation.

Stage 7: Participants' interview to assess acceptability: Once the VIRTUE treatment is complete, all participants from each arm of the trial will be invited to take part in an interview using a short structured questionnaire with a member of the research team. Interviews are designed to explore the acceptability of the study processes.

Stage 8: 3 months follow-up assessment (3 months from randomisation +14 days): The primary outcome measures (cognitiive function) will again be assessed by an independent assessor unaware of the treatment allocation.

Intervention Type

Device

Phase
Phase II

Primary outcome(s)
Current primary outcome measures as of 04/10/2019:
1. Acceptability of the trial to patients measured using a questionnaire within 1 week following the end of the intervention
2. Cognitive function assessed using Cognitive Assessment of Minnesota (CAM) at baseline, the end of the intervention and 3 months after the end of the intervention

Previous primary outcome measures:
1. Feasibility and acceptability of VR-based cognitive rehabilitation in patients with cognitive impairment immediately after a stroke
2. Identification of the optimum dosing of VR-based cognitive rehabilitation

Key secondary outcome(s))
Current secondary outcome measures as of 04/10/2019:
1. Acceptability of the trial to staff measured using a questionnaire following the end of the recruitment in the trial
2. Ability to perform activities of daily living (ADL) assessed using the Nottingham Extended ADL Scale at baseline and 3 months after the end of the intervention
3. Mood assessed using the Hospital Anxiety and Depression Scale (HADS) at baseline and 3 months after the end of the intervention
4. Quality of life assessed using EuroQol at baseline and 3 months after the end of the intervention
5. Arm function using Action Research Arm Test (ARAT) at baseline and 3 months after the end of the intervention

Previous secondary outcome measures:
1. Assess the feasibility of using sham VR as a control in the future phase III RCT
2. Acceptability of VR-based cognitive rehabilitation amongst the staff

Completion date
30/11/2020

Eligibility

Key inclusion criteria
1. Aged over 18 years
2. Have suffered a unilateral stroke (both ischaemic and haemorrhagic as diagnosed by stroke physician) between 1 day to 3 weeks previously
3. No or minor pre-stroke handicap defined by modified Rankin scale score before stroke between 0 and 2
4. MoCA score <26 (out of 30) AND a trained Occupational Therapist has identified that the patient who will benefit from further cognitive therapy

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
40

Key exclusion criteria
1. History of dementia before the stroke
2. Unfit/too ill to receive occupational therapy within 3 weeks
3. Visual acuity <6/60
4. History of epilepsy
5. Bilateral arm weakness or cannot use their unaffected arm
6. Not able/willing to provide informed consent

Date of first enrolment
03/10/2019

Date of final enrolment
31/08/2020

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Countess of Chester NHS Foundation Trust
Liverpool Road
Chester
United Kingdom
CH2 1UL

Sponsor information

Organisation
Countess of Chester NHS Foundation Trust

ROR
https://ror.org/0149cpy58

Funder(s)

Funder type
Government

Funder Name
Innovate UK

Alternative Name(s)
UK Research and Innovation Innovate UK, innovateuk

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during this study will be included in the subsequent results publication.

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		10/03/2022	14/03/2022	Yes	No
Abstract results	Results abstract European Stroke Organisation Conference 2021	03/09/2021	29/03/2023	No	No
HRA research summary			26/07/2023	No	No
Participant	version V5	19/09	04/10		

information sheet		/2019	/2019	No	Yes
Participant information sheet	Participant information sheet	11/11 /2025	11/11 /2025	No	Yes