The Impact of Rehabilitation-oriented Virtual Reality Device in Patients With Ischemic Stroke in the Early Subacute Recovery Phase: Study Protocol for a Phase III, Single-Blinded, Randomized, Controlled Clinical Trial

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ABSTRACT

BACKGROUND AND RATIONALE: Stroke is considered the most common cause of adult disability. Intensive rehabilitation protocols outperform nonintensive counterparts. The subacute stroke phase represents a potential window to recovery. Virtual reality (VR) has been shown to provide a more stimulating environment, allowing for increased patient compliance. However, the quality of current literature comparing VR with standard therapies is limited. Our aim is to measure the impact of VR versus standard therapy on the recovery of the upper limb motor function in patients with stroke in the early subacute recovery phase.

METHOD: This is a randomized, controlled trial that will assign 262 patients to tailor-made standard rehabilitation (TMSR) or TMSR plus immersive VR device. The trial will be conducted in an urban rehabilitation clinic in the United States with expertise in the management of poststroke patients. Patients will be 18 to 70 years of age and in the early subacute period (30-90 days post ischemic stroke). The primary outcome will be the change of Fugl-Meyer Assessment—Upper Extremity (FMA-UE) score, measured at baseline and 13 weeks after randomization. The secondary outcome will be the change in the UK Functional Independence Measure and Functional Assessment Measure (UK FIM-FAM) score at the same time points.

DISCUSSION: If the use of VR in the rehabilitation of patients with stroke proves to have a significant impact on their motor recovery, it will constitute an extremely important step into decreasing the functional impairment associated with stroke and the related health care expense burden.

KEYWORDS: Stroke, virtual reality, rehabilitation, motor recovery, Fugl-Meyer score

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Introduction

Background and rationale

Stroke incidence has been decreasing in the recent years.[1] However, according to the Stroke American Association, the disease burden accounts to approximately 795 000 events occurring every year in the United States alone. This disease also has a tremendous economic burden in the United States, as the estimated direct and indirect costs of stroke, including loss of future productivity, and the nursing homes costs are projected to rise from US $396 billion to US $918 billion from 2012 to 2030.[2] Stroke represents the most common cause of adult disability[3] and second major cause of dementia[4] with some studies showing rates as high as 36% of the affected population ending with any stroke-related disability 5 years after the episode despite state-of-the-art care,[3,4] and rates as low as 26% of patients being able to retain everyday activities.[5] Some data sets reveal rates as high as 80% of all patients with stroke developing some degree of upper limb motor impairment.[6]

The effects of stroke on the upper limb function are a common and significant source of long-term disability. Problems such as paresis, loss of sensation, pain and spasticity in the hand, arm, and shoulder can have multiple consequences in the daily lives of those affected.[7] There are 3 main functional consequences of impairments on upper limb function: (1) learned nonuse, (2) learned bad-use, and (3) forgetting as determined by behavioral analysis of tasks.[8]

Recovery after stroke, although limited, occurs in a nonlinear, logarithmic pattern.[9,10] Significant functional recovery may develop in the first 3 months following the episode[11] with spontaneous mechanisms playing an important role, especially during the first month.[12] Afterward, recovery is associated with cerebral plasticity and cortical reorganization, in great part stimulated by rehabilitation programs.[13] In this regard, intensive rehabilitation programs outperform less-intensive regimens, allegedly due to better stimuli in the reorganization and adaptive mechanisms involved.[12] Standard rehabilitation protocols are considered as less intensive given their repetitive nature, poor cognitive stimuli, and lack of direct feedback stimuli.[14] In this scenario, the use of VR is a relatively novel adjunct, which can compensate for the lack of intensive treatments. Recent reviews and meta-analysis summarize the recent results of the use of VR as a facilitator on motor rehabilitation programs, with positive results.[11,15] Virtual reality adds on rehabilitation by providing a computer-generated environment that allows the user to interact with it by standard devices or special haptic devices such as wired gloves.[16] There is, as of now, moderate quality evidence sustaining the use of VR as an add-on to standard therapy regimens showing significant results.

However, the available data so far come mostly from studies on chronic patients with stroke, ranging from 6 months to more than 3 years after the event.[11] Most of the studies used the following definition: acute phase within the first month, subacute between 1 and 6 months, and chronic phase if longer than 6 months after stroke occurrence.[17,18] In 2017, the Stroke Recovery and Rehabilitation Roundtable Taskforce proposed a new time frame for stroke recovery with the aim of improving and facilitating the research in this field.[19] The new consensus describes 4 phases: hyperacute (0-24 hours), acute (1-7 days), early subacute (7 days to 3 months), late subacute (3-6 months), and chronic (>6 months). For the purpose of this protocol, we would use the term "early subacute" in reference to patients 30 to 90 days after the stroke (previously known as subacute recovery phase). Although there is evidence supporting that the potential for recovery is more profound during the early subacute period,[11,20] studies are underpowered, have small populations, or are too heterogeneous, resulting in lower quality evidence.[21] In this group of patients, the data available are limited and so far as the combination for other novel therapies such as transcranial magnetic stimulation,[22,23] focused on arm support[24] or phase II trials.[25,26] Also, most trials give little information about how the intervention and controls are planned and fewer have tools to guarantee equivalence between both arms.

Therefore, we aim to execute a larger trial to assess whether the Interactive Rehabilitation and Exercise program (IREX), a rehabilitation-oriented VR device, delivering standard tailor-made rehabilitation, can provide better recovery of the upper limb motor function when used as part of the therapeutic regimen for patients with ischemic stroke in the early subacute recovery phase.[27]

Objectives

To estimate the extent to which the addition of VR to a patient tailor-made standard rehabilitation (TMSR), in comparison with patient TMSR alone, affects the upper limb motor recovery in patients with early subacute stroke.

Our hypothesis is that the addition of IREX as a facilitator to patient tailor-made physical therapy improves motor function and overall disability in patients with ischemic stroke and upper limb impairments in the early subacute recovery phase more than the standard rehabilitation, as measured by Fugl-Meyer Assessment—Upper Extremity (FMA-UE) and UK Functional Independence Measure and Functional Assessment Measure (UK FIM-FAM) scores.

Methods

Trial design

This is a randomized, single-blinded, phase III–controlled trial of a VR device (IREX)-guided rehabilitation program for patients with ischemic stroke and upper limb motor impairment in the early subacute recovery phase, with a 1:1 allocation ratio to either TMSR alone or TMSR delivered through IREX for a total duration of 13 weeks.

Table 1. Eligibility criteria.

INCLUSION CRITERIA
Patients presenting with first stroke episode confirmed by CT or MRI (G1)
Outpatients only (G1)
Age between 18 and 90 years (G1)
30-90 days poststroke patients (G1) regardless of previous rehabilitation protocols exposure
Patients with stroke with a motor compromise that must include but is not limited to upper limb only (G1)
Successful tolerance on IREX trial run (G2)
EXCLUSION CRITERIA
Non-English speakers: defined as a patient who cannot communicate in English without an interpreter (G1)
Significant visual impairment: legally blind patients and untreated patients with cataracts, retinal detachment, and any other visual acuity/refractive defects as determined by their past medical history (G1)
Significant cognitive impairment (score of 24 or lower on the mini-mental state examination) (G1)
Spasticity as measured by the Modified Ashworth scale >2 points (G1)[a]
Diagnosis of hemineglect syndrome, as determined by Sunnybrook Neglect Assessment Procedure (SNAP) score >5 (G1)[a]
Any intracranial pathology other than stroke (that lead to upper limb involvement) (G1)
Reported vertigo or dizziness (G1)
Major depression as defined by a score ⩾20 on Patient Health Questionnaire 9 assessment (PHQ-9) with daily life activities impairment
Degenerative changes: progressive neurodegenerative diseases, motor deterioration, joint stiffness, amputations, and auditory deficit (G1)
Epilepsy (2 occurrences in last 6 months) (G1)
History of previous stroke (G1)
Patients who do not wish to stop any current rehabilitation program that involves the upper limb (G1)
Inability to adapt at least 80% of the rehabilitation protocol to IREX to do the VR protocol (G2)

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; IREX, Interactive Rehabilitation and Exercise program; SNAP, Sunnybrook Neglect Assessment Procedure; VR, virtual reality.
[a]Please see Supplementary Material for further explanation.

Study setting

The study will take place in an urban rehabilitation clinic of a large academic center in the United States with expertise in the management of poststroke patients. There will only be 1 intervention center for both arms of treatment. The center will be chosen based on easy accessibility for all participants, in an area close to multiple other hospitals and outpatient clinics.

Eligibility criteria

Inclusion and exclusion criteria are divided into 2 categories (Group 1 and Group 2) and will be evaluated at two different times during the recruitment period. G1 criteria will be evaluated first. This group includes patient status, limitations, neurological evaluation and questionnaires. Afterward, patients will be exposed to a trial run for the IREX device, which will be further detailed below. Those able to complete the trial will have their intervention program planned, and should the final plan be adaptable to IREX in at least 80% of its total length will proceed to randomization. The trial and after planning evaluation are, therefore, criteria to be accessed after the initial inclusion and are denominated group 2 (G2). The inclusion and exclusion criteria are detailed in Table 1. Both will be assessed at the first visit at the rehabilitation center, according to the workflow shown in Figure 1.

Organization of the intervention groups

Both TMSR and IREX-BASED TMSR teams will be formed by a multidisciplinary team composed of a physical therapist with experience in rehabilitation, a neuropsychologist, and an occupational therapist. Each group will be assigned to a rehabilitation coordinator: a registered nurse with special training who will follow the program from admission to discharge. TMSR and IREX-based TMSR teams will have assistance of a technician trained to use the device as well as maintain and

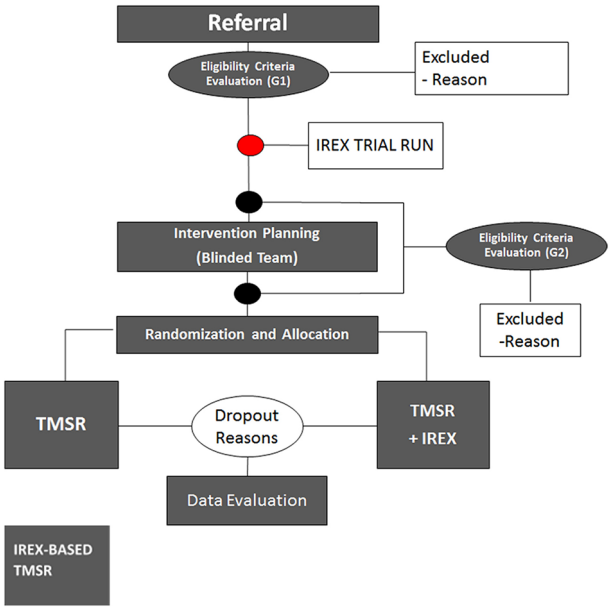

Figure 1. Study workflow. TMSR indicates tailor-made standard rehabilitation; IREX, Interactive Rehabilitation and Exercise program.

provide assistance when needed. This organization is adapted from the team setup used in the Mayo Clinic and John Hopkins rehabilitation centers.[28,29]

Intervention

Eligible patients will be randomly allocated to upper limb TMSR alone or upper limb TMSR delivered through a VR device (IREX). Tailor-made standard rehabilitation is a 35-minute session, 3 times per week, for 13 weeks, with 150 to 180 movements per session, ideally every other day.[30] Baseline data and scores of both groups will be evaluated before the first intervention.

Poststroke rehabilitation is multidisciplinary and individualized.[31] Our purpose is to use standardized exercises of repetitive tasks and strength training tailored to each patient.[32] The training will involve task-related training (TRT) and progressive resistance exercise (PRE) individualized to the motor function of the patient. Both TRT and PRE have shown individual and combined benefits for rehabilitation.[32] TRT using goal-directed, intentioned movements induces brain plasticity and is expected to promote recovery of reaching in hemiparetic subjects. The exercise involves reaching to objects placed across the workstation. Patients affected upper limb reaches to touch or grip the objects of varying sizes, shapes, and weights. Objects have to be picked up from different quadrants of the workstation and also from the floor, and adjacent stools and these actions have to be of varying amplitudes. Progressive resistance exercise will involve the entire upper limb pulls with the help of resistance bands. Actions will be carried out in similar planes and distances to those in TRT. Patients will grasp onto one end of the resistance band with the opposite end fixed on a wall at the same level as the patient's elbow. Four directional actions will be encouraged. These will include movements of shoulder extension, flexion, abduction and adduction, and rotations, as well as elbow extension, flexion, and rotations.

A team that will be blinded to the allocation scheme will evaluate and elaborate the physical therapy program for both study arms. The regimen will serve both for control and for adaptation to the IREX of the intervention group. The VR program will have vocal prompts and assistance when required.

For the upper limb rehabilitation, the patients will be seated in an armless chair with their trunk unrestricted. Training will involve only the paretic upper limb. Patients will be instructed to move at preferred speed and to increase the speed as the training advances. Ensuring training involves more complex tasks if the session takes less than 35 minutes. Care will be taken to observe for any compensatory actions and accordingly advice will be given (for instance, standing next to a wall would help to curb compensatory abduction and rotation of shoulder while reaching out). The TMSR-alone group will be allowed to use building blocks, bands, and other general devices as to simulate what happens on state-of-the-art rehabilitation programs; however, no novel or under study device such as electrical external stimulation will be allowed. For the IREX group, the standardized upper limb VR games "birds and balls, coconuts, drums, juggler, and conveyor" will be used as needed and adapted to the patient protocol. Parts of the protocol not adaptable to IREX will be executed the same way as TMSR.

If participants express their desire to quit the protocol, the study coordinator will interview this patient as to determine the reasons behind their decision and will try to provide a solution to any inconvenience that may cause the dropout. If the participant insists of changing the study arms or leaving the protocol, they will not be allowed to switch arms, but they will be strongly advised to continue the rehabilitation protocol through the standard of care.

To reduce performance bias and stimulate participation and adherence, we will offer to the control group 5 IREX sessions at the end of the study and after the final evaluation. Also, while highly encouraged to do the rehabilitation sessions every other day, patients will have the option of choosing whichever 3 days in a given week at their convenience.

There will be no cost to the subjects taking part in the trial. Transportation to the rehabilitation center and back will be provided to every participant. As a mean to ensure adherence at the rehabilitation sessions, a telephone reminder will be conducted the day before, stating the date, place, and time of their session. Engagement of close relatives will be encouraged to provide support to the participants. Furthermore, if any of the participants does not show up to an appointment, the study coordinator will reach them via phone call as to determine the cause of the absence and potential solutions. If patients agree to continue, they will be rescheduled within the same week.

Due to the high impact of attendance on the individuals' progress and motor recovery, a patient will only be considered adherent by attending at least 80% of the sessions.

Patients who willingly accept to take part in our trial will be asked to stop participating in any other rehabilitation programs that involve the upper limb. For any other motor deficit (lower limb) or any other neurological deficit, the rehabilitation will be delivered through the usual standard of care in the study center with the needed rehabilitation personnel. Patients will continue to follow up with their neurologists and primary care physicians per standard of care, independent of the study arm that they were assigned to.

Speech-language pathologists, psychologist, respiratory therapists, vocational therapists, social workers, and registered dietitians may be assigned by the assisting neurologist outside of the study protocol, to cover other disabilities as needed, but this will not be covered under this research proposes and must be done on separate times with the intervention protocol.

Outcomes

Primary outcome. The mean difference will be evaluated in between the 2 treatment arms in the FMA-UE score at 13 weeks after randomization. Fugl-Meyer Assessment (FMA) scale is a validated tool widely used for motor function assessment in patients with stroke.[33] As a continuous outcome measure, it has good correlation with the changes in motor impairment.[34] The motor score in this scale ranges from 0 (hemiplegia) to 100 points (normal motor performance), divided into 66 points for upper extremity and 34 points for the lower extremity.[35] For the means of the primary outcome, only the 66 upper extremity points will be considered (FMA-UE).

Secondary outcome. For secondary endpoint, participants will be scored according to the UK FIM-FAM score at baseline and at the end of the intervention. We will evaluate the mean difference in the overall score. Functional Independence Measure (FIM) is an 18-item global measure of disability where each item is scored on 7 ordinal levels. Functional Assessment Measure (FAM) adds 12 items specifically addressing cognitive and psychosocial function. Therefore, the UK FIM-FAM score will essentially rate independence for daily activities. Scoring goes from 1 (total assistance) to 7 (complete independence) and treatment success will reflect the improvement from the baseline score to the end of the intervention score.[36] We will also make use of the complete FM assessment scale as a secondary outcome, as part of a broader evaluation. The change from baseline to 13 weeks will be reported for the FMA-UE scale and for the FIM-FAM score.

Another included secondary outcome is the patient perception of the intervention (IREX). This outcome will be evaluated by using the System Usability Scale at the end of the study. This will be evaluated as proportions over the final score value, using 68 points as the threshold. The goal to compare groups is to evaluate whether IREX has a similar usability than standard rehabilitation tools and programs. The scale consists of a 10-item questionnaire with response options going from "strongly agree" to "strongly disagree." The scale goes from 0 to 100 and a score above 68 gives an above average usability for the system.[37]

Finally, we would like to assess the participant satisfaction with the use of VR. For this purpose, we chose 2 tests: the Visual Analogue Scale (VAS) for both groups and the User Satisfaction Evaluation Questionnaire (USEQ) for the IREX-based TMSR group only. The application of VAS would allow to compare the overall satisfaction with the intervention in each group and to compare both results. The VAS scale has been widely used to measure patients' satisfaction and it is less vulnerable to bias and confounders.[38] Patients will be asked to rank their level of satisfaction after completing their last session of physical therapy from 0 (completely unsatisfied) to 10 (completely satisfied). The USEQ was proposed in 2017 as a new tool to evaluate the satisfaction component of usability.[39] This questionnaire was tailored specifically for its use with VR devices. This instrument consists of 6 questions with a 5-point Likert-type scale. Scores can range from 6 (lowest satisfaction level) to 30 points (highest satisfaction level). All patients in the TMSR + IREX-based TMSR group will be asked to answer the questionnaire at the end of their last session of physical therapy. The results of the questionnaire will be reported as the mean value of all scores obtained, as previously done by the creators of the scale.

Participant timeline

After the enrollment in the study, each patient will complete 13 weeks of TMSR or TMSR + IREX-based TMSR. All the follow-up appointments with be scheduled at the second session (Figure 2). The assessments (FMA-UE scale and the UK FIM-FAM) will be done at baseline (during the second session) and at 13 weeks (prior to their last session).

Sample size

For sample size calculation, standard deviation will be exploited from a recent meta-analysis on a conservative approach.[40] Accepted value will be at 10 points for both groups.[40] For sample size estimation, we will use alpha of 0.05 and power of 90% to identify a 4.25 points difference in the main outcome.[41] The attrition rate of VR studies in stroke varies significantly.[40] A meta-analysis suggests that only 1 out of 17 studies have a dropout rate greater than 10%.[42] Therefore, we assumed a conservative attrition rate of 10%. Considering such specifications, we estimated that a total of 262 patients will be needed, with 131 on each arm.

	STUDY PERIOD				
	Enrolment	Allocation	Post-allocation		
TIMEPOINT	$-t_1$	0	t_1	t2- t12	t_{13}
ENROLMENT:					
Eligibility screen	X				
IREX trial run	X				
80% adaptability of the rehabilitation protocol	X				
Informed consent	X				
Allocation		X			
INTERVENTIONS:					
TMSR			X	X	X
IREX-BASED TMSR			X	X	X
ASSESSMENTS:					
FM-UE scale			X		X
UK FIM-FAM			X		X
SUS SCALE					X
USEQ SCALE					X

Figure 2. Schedule of enrollment, interventions, and assessments. IREX indicates Interactive Rehabilitation and Exercise program; TMSR, tailor-made standard rehabilitation; FMA-UE scale, Fugl-Meyer Assessment—Upper Extremity scale; UK FIM-FAM scale, UK Functional Independence Measure—Functional Assessment Measure; SUS, System Usability Scale.

Recruitment

We anticipate the recruitment period to last 30 months. We will perform individualized visits to invite all the neurologists and primary care providers available within 1-hour drive from the intervention center. These visits are meant to engage their participation by referring all potential candidates for the selection process. We will also provide them with a complete list of the inclusion and exclusion criteria to avoid unnecessary mobilization of patients and patient-directed flyers with a brief explanation of the study. Once a patient is considered eligible for the study, the neurologists and primary care providers will refer the patient to our intervention center. All the patients with stroke already going through rehabilitation in the intervention center will be systematically evaluated for eligibility to be included in the study. The patients in the acute phase, once they pass their 30-day poststroke mark, will be invited to participate in the study. By the time a new patient presents to their first appointment, theywill go through the inclusion and exclusion criteria, and if they are found eligible to be enrolled in the study, they will be invited to the IREX trial run.

This trial run will consist of 1 session of 30 minutes where patients will perform several exercises without any therapeutic value. The trial session is oriented to evaluate whether the patients can tolerate the IREX device. It is not aimed to decrease patient disabilities, but to assess the device acceptance by repeating games, without baseline strength or repetitions, using the planned intensive regimen length.

Patients who are found noneligible in this stage will be directed to start or continue their rehabilitation program outside of the study. All the patients who were able to tolerate the IREX trial run will have their rehabilitation protocol tested for IREX adaptability. Only the patient who has a protocol 80% or higher adaptable to IREX will undergo randomization. The patient who does not have a protocol at least 80% adaptable to IREX will be directed to start or continue their rehabilitation program outside of the study. This process is expected to be completed in the first appointment.

At the second appointment, all the patients who had the rehabilitation protocol adaptable to IREX will be approached by the research assistant to give consent for the study. Informed consent will be collected prior to the allocation and after explaining the nature of the study, information regarding IREX therapy, potential benefits, and side effects with the purpose to solve any doubts that the participants may have and set realistic expectations from this intervention. Clinical site staff will be prepared to answer any additional questions or complaints about the treatment either in person or by phone.

Finally, after the randomization, patients who were allocated to the IREX arm will undergo 1 session of usage orientation to procure the familiarization with the device and to reduce noncompliance due to inadaptation. This session lacks any therapeutic value. Their first rehabilitation session will take place right after the orientation session. The patient randomized under the regular rehabilitation protocol will have their first session on the same day.

Allocation

Allocation will be achieved through a computer-generated permuted block randomization sequence with random block size of 4 and 6. The blocking sizes and restrictions will be concealed from the enrollment team to ensure concealment. A Central Service Center will have the allocation scheme. When a new eligible participant signs the informed consent, the research assistant will call the Central Service Center to obtain the corresponding next allocation placement. Participants will be randomly allocated to either treatment or control groups in a 1:1 allocation according to the sequence. After the trial run and protocol planning, patients will undergo randomization and will then be informed to which treatment arm they were assigned to.

Blinding

The data collectors, outcome assessors, and the data analysts will be blinded throughout the intervention process and until the end of the data analysis. Neither patients nor the therapists can be blinded as they will be exposed to the IREX device during the G1 selection process regardless of their final allocation. Regarding family members or guardians, it may be necessary to reveal the allocation to enhance adherence and would be done for this purpose only. The patients will be reminded at every session not to disclose their allocation to the treating physicians or outcome assessors.

Blinding assessment. Blinding assessment would take place after the study is over. A survey would be handed to the outcome evaluators after the last evaluation. They will be asked to determine the treatment allocation.[43] Blinding would be considered successful if the percentage of "do not know" is the highest or if correct and incorrect guesses are balanced.

Data collection

A predetermined spreadsheet with the baseline characteristics variables will be used to collect the data and it will include age, sex, race, education level, sociodemographics/employment level, body mass index (BMI), tobacco-use status, and Charlson Comorbidity Index (diabetes mellitus, liver disease, malignancy, AIDS, moderate-to-severe chronic kidney disease, congestive heart failure, myocardial infarction, chronic obstructive pulmonary disease, peripheral vascular disease, cardiovascular accident [CVA] or transient ischemic attack (TIA), dementia, hemiplegia, connective tissue disease, and peptic ulcer disease). Baseline data on FMA-UE score, the FIM-FAM assessment, and the complete FAM will also be collected.

All the outcome data will be collected at 13 weeks after starting the intervention. This will include the FMA-UE score, the FIM-FAM assessment, the complete FAM and the System Usability Scale (SUS) score. For those taking part in the project as assessors, they will receive training with the intended scores, through a 2-week period using those scores for patients undergoing standard rehabilitation on the center. Data from those patients will be discarded as they are not part of the study, after the questionnaires will be reviewed and appropriate feedback will be provided to the physical therapists.

To promote participant retention and complete follow-up, the following will be taken into account: all questionnaires are intended to be filled during the rehabilitation sessions (1 and 13 for both groups). The demographic status of participants will be regularly updated at the time of their visit.

All data will be entered electronically to a locked/secured database. Access to the data will be limited to research personnel only. Administrator access rights will be limited to the principal investigators. Activity is regulated using identification codes and passwords. Study forms/questionnaires will be printed and completed forms will be kept in a locked file cabinet located in the research assistant office. Names will be replaced with encoded identifiers, with the key kept in a locked file cabinet. The data with encoded identifiers will be given to the biostatistician for the final data analysis. Data will be maintained in storage for a period of 11 years after the study is completed. Electronic backup of the data will occur every week.

Data management

Questionnaires will be collected by a research assistant who does not have access to the randomization scheme, who will add the data to an online Excel® spreadsheet daily. The filled cells will be automatically locked, and conditional formatting implemented to avoid wrong data imputation. A revising committee will check for data integrity weekly and report any imputation mistake for correction. Patients will be identified by a number that will correspond to the randomization sequence developed by the statistics team. At the end of the study, the Excel spreadsheet will be unlocked to an allocation blinded statistician to perform the required analysis, after which the groups will be unblinded.

Statistical methods

The primary analysis of all primary and secondary outcomes will be on an intention-to-treat (ITT) basis. A secondary "per-protocol" analysis will be completed including only patients adhering to the study protocol who have met at least 80% of their visits. All missing data will be replaced with substitutions or imputations. The last observation carried forward will be used to replace the missing data if it exceeds a 5% threshold. Sensitivity analysis will be performed using full data only.

Descriptive statistics will be given for all data collected. Categorical variables will be reported as counts and percentage frequencies. Continuous variables will be reported as either mean ± SD or the median and range or interquartile ranges according to data normality. The 2 randomization groups will be examined for all variables. Categorical variables will be examined using Fisher exact test or Pearson chi-square tests where appropriate. For continuous data, normally distributed variables will be examined using 2-sided t tests. Nonnormally distributed variables will be examined using nonparametric Wilcoxon rank tests. Normality will be assessed both by histogram analysis and Shapiro Wilk testing.

Due to the nature of the FMA-UE scale, it will be ascertained as a continuous outcome.[33] The primary outcome will be examined between the 2 randomization arms with either a *t* test or a Wilcoxon rank test depending on the normality assessment of the changes. Within each arm, the paired difference between baseline and 13 weeks will be examined with a sign test to see whether the change is different than 0. As for secondary outcome evaluation, we chose to treat the UK FIM-FAM score as ordinal,[35] as such comparing results with Wilcoxon rank test, whereas the System Usability Scale score will be categorized according to the accepted clinically relevant cut-off of 68 points and evaluated using chi-square test. In case we find unbalances in the baseline characteristics, multivariate models will be used to adjust for key confounders. All evaluations will be performed in Stata IC 15® with an alpha of 0.05.

For the analysis of the VAS score, we will determine the distribution of data with histograms analysis and Shapiro Wilk test. If normally distributed, the mean of both groups will be compared with the 2-sided Student *t* test. If nonnormal distribution is found, the median of both groups will be examined with the nonparametric Wilcoxon rank test.

Bias

Our study might be subjected to a low degree of selection bias as only the patients who can tolerate the device (IREX) will be included in the study. This could affect the generalizability of the results. We took measures to deal with attrition bias such as reminder calls the day before each intervention and by providing transportation to the patients that needs it. Therefore, we do not expect to have a high percentage of dropouts. Perception bias could be introduced if outcome evaluators were to become unblinded during the first or second evaluation. If this happens during the first evaluation, the evaluators are instructed to report their unblinding to the study coordinator so they can be reassigned to another patient. We will not change the evaluators if the unblinding happens by the end of the study. Although recovery is a measurable endpoint, the scores are not immune to perception bias and, in this regard, the novelty of the intervention, as well as patients' perceptions might add to reported recovery and subsequent bias. As possible unblinding and in-between patient's interaction might add to this effect, extra steps have been taken, as described, to avoid these issues.

Due to the need of a trial run, all patients will be exposed to IREX prior to intervention, this could generate a perception bias and strength placebo effect favoring the IREX arm; however we deemed this section worthy such risk as to ensure patients' safety.

Discussion

Previous studies have shown that nonimmersive VR interventions are not significantly more beneficial when compared with conventional rehabilitation regimens.[21] However, it was suggested that immersive VR systems, such as IREX, could enhance the recovery of the upper limb motor function as they provide with a wider range of stimuli and a more interesting and engaging environment for the patients, which could also play an important role in the adherence to treatment.[21,44]

Two studies suggest that immersive VR rehabilitation protocols improve the motor function through neuroplasticity and cortical reorganization. Jang et al[45] found statistically significant difference in Laterality Index and locomotor recovery of the areas of interest when compared with the control group. The second study reported decreased ipsilateral aberrant cortical activation while promoting contralateral cortical activation that would translate to improved motor function in the affected limb.[46] Although both studies have small sample sizes, they account for the first evidence of the mechanisms behind VR-induced motor recovery.

VR-based rehabilitation protocols provide with a safe and more appealing environment for patients with stroke. It also allows to train patients in real-life task that could not be

performed otherwise (like crossing the street) and the opportunity to do so without supervision once the patient feels comfortable with the device, increasing their level of independence.[15]

By the addition of VR as a facilitator, we expect to be able to diminish chronic disability, increase patient's independence, and diminish chronic impairments related to stroke, as evaluated by rehabilitation-specific scores. If the use of VR in the rehabilitation of patients with stroke proves to have a significant impact on their motor recovery, it will constitute an extremely important step into decreasing the functional impairment associated with stroke and the related health care expense burden.

VR devices will become of more widespread use and will potentially be adapted to benefit other chronic diseases that are associated with significant economic burden. The rigorous methodological process and the large sample size of this trial can provide high-quality evidence toward such novel intervention. Also, by developing a solid standard for the use of such devices, we aim to provide the basis for future VR cost-benefit evaluations, the final step needed to include such technology into rehabilitation facilities.

Harms and data monitoring

Harms associated with this intervention are described as headache, nausea, and/or fatigue episodes that resulted in patients looking for medical care at their neurologists or primary care providers. There are no other possible harms associated with the intervention when compared with the standard therapy. Given the low-risk profile and relative short duration of the intervention, we do not plan to execute an interim analysis. Therefore, a Data Monitoring Committee (DMC) is not needed.

Auditing

The auditing process would be handled by the corresponding Institutional Review Board (IRB) committee as per their annual revision of protocols.

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Author Contributions

NA developed the study research question; VAQM and OGR were the overall project coordinators; AH was the overall project mentor; OGR is the corresponding author and served as main reviewer during the submission process; OGR, MS, VAQM, LCS, and SD were group coordinators for the project; AS, GC-T, G, LPS, RN, ATS, MT, and RM-V assisted in mentoring the project development; and AGSR, MS, RF, ATS, and RM-V planned the statistical planning and development. All authors gave significant collaboration toward methodological planning and overall manuscript writing. AS, GC-T, JM, JML, LPS, LCS, MS, RN, RM-V, RF, SD, SHH, SA, UA, WAC, ATS, AF, AJ, MSMdOP, AGSR, RAG, MT, HN, and MZS contributed to the study protocol in equal parts.

Authorship Eligibility Guidelines

As a multiauthor work, authorship eligibility was evaluated according to the proposed score by Petroianu, Andy in 2002. This score prioritize a punctuation-based scale with more points being granted to the development of the idea behind the project and development of a methodological structure (6 points), followed by manuscript writing, coordination, and mentoring work for the overall manuscript (5 points); coordination for the involved work groups, literature review, and key additions or proposals (4 points); data collection, tool development pertinent to the work development, statistical analysis, mentoring or guidance for the manuscript writing/revision, and preparing scientific presentation (3 points); presenting the work on scientific meetings (2 points); and finally minor additions or suggestions (1 point). All collaborators with 7 or more points were eligible as authors. All cases where there were doubts within the punctuation were decided by the first author and mentor.

Access to Data

Access to the final data set and disclosure of contractual agreements that limits the access to information is to be determined by the group of investigators who would run the trial in the future.

Ancillary and Posttrial Care

As per the literature review, we do not expect any additional harm to be inflicted on the subjects in the intervention group when compared with the standard therapy. For this reason, we do not see the need to plan for compensation.

Confidentiality

All collected data will be deidentified for the purpose of storage, processing, and interpretation. The randomization sequence will not be disclosed to any of the involved parts until the end of the trial.

Consent for Publication

All the authors were in agreement and consented for this final version of the manuscript to be submitted for publication.

Ethics Approval and Consent to Participate

Our study protocol was developed through an international collaboration as part of a didactic learning program and it has

been peer-reviewed by multiple scientists affiliated with Harvard Medical School and Harvard T.H. Chan School of Public Health. We intend to use the protocol as a methodological contribution to science rather than a study proceeding to be applied by the present group of authors. Our study protocol provides guidance for clinical practice and could be used by other groups in the neurology and rehabilitation medicine fields. For these reasons, we consider that ethics approval is not mandatory. If future potential authors wish to proceed to start the trial, they should seek for Institutional Review Board (IRB) approval at their corresponding institution. They would also be in charge of determining the personnel who would consent patients and other logistic details to their convenience.

Dissemination Policy

The authors of this protocol have no restrictions regarding publication of the trial results to participants, health care professionals, the public, and other relevant groups.

Informed Consent Materials

We do not count with an informed consent form for this protocol yet. The authors in charge of running the trial are free to customize an informed consent according to the specifications of the IRB committee.

Protocol Amendments

Any plans for communicating important protocol modifications to relevant parties will be discussed with the IRB committee when the trial takes place.

Protocol Version

Last version: November 28, 2019—reviewed version.

Trial Registration

Our study protocol was developed through an international collaboration as part of a didactic learning program and it has been peer-reviewed by multiple scientists affiliated with Harvard Medical School and Harvard T.H. Chan School of Public Health. We intend to use the protocol as a methodological contribution to science rather than a study proceeding to be applied by the present group of authors. For these reasons, the protocol has yet to be registered.

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Supplemental Material

Supplemental material for this article is available online.

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