Taylor & Francis
Taylor & Francis Group

Disability and Rehabilitation

ISSN: 0963-8288 (Print) 1464-5165 (Online) Journal homepage: www.tandfonline.com/journals/idre20

Immersive virtual reality for upper limb rehabilitation in people with MS: a randomised, controlled feasibility study

Amy Webster , Matthieu Poyade , Elaine Coulter , Niall John James MacDougall , Karen Brown & Lorna Paul

To cite this article: Amy Webster , Matthieu Poyade , Elaine Coulter , Niall John James MacDougall , Karen Brown & Lorna Paul (26 Jun 2026): Immersive virtual reality for upper limb rehabilitation in people with MS: a randomised, controlled feasibility study, Disability and Rehabilitation, DOI: 10.1080/09638288.2026.2676065

To link to this article: https://doi.org/10.1080/09638288.2026.2676065

DISABILITY AND REHABILITATION
https://doi.org/10.1080/09638288.2026.2676065

Taylor & Francis
by informa

RESEARCH ARTICLE

Immersive virtual reality for upper limb rehabilitation in people with MS: a randomised, controlled feasibility study

Amy Webster[a], Matthieu Poyade[b], Elaine Coulter[a], Niall John James MacDougall[c,d,e], Karen Brown[f] and Lorna Paul[a]

[a]School of Health and Life Sciences, Glasgow Caledonian University, Glasgow, UK; [b]School of Innovation and Technology, Glasgow School of Art, Glasgow, UK; [c]Department of Neurology, Institute of Neurological Sciences, Queen Elizabeth University Hospital, Glasgow, UK; [d]Department of Neurology, University Hospital Hairmyres, East Kilbride, UK; [e]Anne Rowling Regenerative Neurology Clinic, University of Edinburgh, Edinburgh, UK; [f]Stroke Neurological Rehabilitation Teams, NHS Lanarkshire, North Lanarkshire, UK

ABSTRACT

Purpose: To investigate the feasibility of an eight-week immersive virtual reality (VR) intervention using co-produced games for upper limb (UL) rehabilitation in people with multiple sclerosis (pwMS).

Methods: In this multicentre, two-armed randomised controlled feasibility study, participants were randomised to either an intervention group involving VR co-produced games, 30 min, twice/week, for eight weeks, or to a control group of usual care. A mixed methods approach was undertaken, collecting feasibility data, UL outcome measures, and conducting post-intervention interviews.

Results: Nineteen pwMS were recruited (intervention $n=11$, control $n=8$), with a recruitment rate of 3.2 participants/month. Adherence was good with 87% (±12%) session completed, with two dropouts both in the control group. Only minor adverse events were reported ($n=9$), such as fatigue and UL pain. Participants reported high levels of satisfaction and good usability of VR games. Thematic analysis revealed participants enjoyed the distraction and atmospheres that immersive VR provided, and believed the games were fit for purpose with the majority of participants reporting improvements in their UL function.

Conclusions: Immersive VR is feasible and safe for pwMS. Future work should refine recruitment strategies, develop VR games for long-term application and explore the clinical and cost effectiveness of this approach.

ARTICLE HISTORY
Received 29 April 2025
Revised 12 May 2026
Accepted 13 May 2026

KEYWORDS
Virtual reality; multiple sclerosis; upper limb rehabilitation; immersive virtual reality; serious games

Introduction

Multiple sclerosis (MS) is a chronic and inflammatory demyelination disorder of the central nervous system, which is estimated to affect 2.8 million worldwide [1]. People with MS (pwMS) have varied symptoms, but typically have some motor, sensory or cognitive dysfunction, with a progression of disability [2]. Upper limb (UL) problems are common in pwMS, even within individuals with lower levels of disability [3], and become increasingly prevalent and disabling as the disease progresses [4]. This is a particular challenge due to the increased reliance on the UL for walking aids and transfers as disability level increases [5].

It is difficult to accurately determine the percentage of pwMS who have some form of UL dysfunction. Bertoni and colleagues [4] reported that 75% of pwMS had dysfunction in both ULs as measured by the Nine Hole Peg Test, 44% had reduced UL strength and 34% had reduced hand grip in both ULs. Newsome and colleagues [6] similarly reported dysfunction in terms of dexterity (45%), grip (31%) and pinch strength (26%). Impaired UL function can have a significant effect on Activities of Daily Living (ADLs) (including dressing, grooming and eating), quality of life, social interactions and employment [5,7].

CONTACT Amy Webster Amy.Webster@gcu.ac.uk School of Health and Life Sciences, Glasgow Caledonian University, Cowcaddens Road, Glasgow, G4 0BA, UK

Supplemental data for this article can be accessed online at https://doi.org/10.1080/09638288.2026.2676065.

In addition, UL impairment increases dependency on others, can negatively affect self-esteem [8], is associated with symptoms of depression [9] and higher healthcare costs [10].

There is strong and compelling evidence of the benefits of exercise training for the ULs in pwMS, although the evidence base is smaller than that for the lower limbs [11,12]. Notably there is a dose-response relationship between the intensity of exercise and outcome; with higher doses of exercise being associated with better outcomes [13]. Engagement and adherence to rehabilitation, especially UL rehabilitation/exercise, which pwMS report neglecting due to lack of motivation, is challenging [14]. Thus, finding effective, enjoyable and motivating approaches to support pwMS to undertake UL exercise/rehabilitation is important especially due to the variable, unpredictable, progressive and long-term nature of MS [15].

Virtual Reality (VR) may provide a solution to improving exercise adherence. VR provides digital simulations of real-world scenarios or uses immersive video games, in which the user can interact with objects displayed in virtual environments [16]. VR games can "disguise" therapeutic exercises due to the various gamified elements, such as scoring, incentives, rewards, feedback and competition, in order to increase engagement and motivation, and provide a more enjoyable experience of rehabilitation [17]. There is also an element of escapism, with VR transferring the user into different virtual environments, which can feel real through immersion [18]. The level of immersion can vary within VR systems, with low immersion typically displaying virtual environments monoscopically on computer monitors; whereas fully immersive systems instead use headsets, known as head mounted devices (HMDs) [19]. Fully immersive VR is suggested to increase engagement and lower perceived effort compared to lower immersive VR [20,21] however, there is a lack of evidence within the MS population.

The relatively low cost and high availability of VR headsets has increased interest in the use of VR for people with neurological conditions; primarily in stroke [22,23] but also in Parkinson's, spinal cord injury, and to a lesser extent MS [24,25]. Our systematic review investigating VR interventions for UL function for pwMS included 10 articles and provided some, but limited, evidence that VR is effective in improving motor function in the ULs. However, there was no clear consensus on which VR based approaches are the most effective, the effect of immersion, or the optimum intervention dose [26]. There are now a number of recently published studies investigating the use of immersive VR for UL rehabilitation in MS, showing limited preliminary evidence for improving UL outcomes [27,28]. Building upon our initial review, we have co-produced bespoke VR games for pwMS [14]. The VR games were then iteratively developed with feedback from people with MS and specialist clinicians. Participants were generally positive about the potential of VR for UL rehabilitation and provided suggestions for development and deployment of VR, which we incorporated into a VR intervention. The aim of this study therefore was to investigate the feasibility of an eight-week VR intervention, of co-produced games, on UL function in pwMS.

Materials and methods

This study followed convergent mixed methods design following the guidance of the NIHR and MRC framework for developing complex interventions [29].

The study was reviewed and approved by the West of Scotland NHS Research Ethics Committee (Ref: 22/WS/0049) and registered on clinicaltrials.gov (identifier: NCT05320237). This randomised, controlled feasibility study involved an intervention group and a control group, and aimed to recruit up to 30 participants. Although, determining recruitment rates was an outcome, the sample size was based on a recruitment rate of 4–5 participants per month for six months. To be included in the study participants were required to be over 18 years, with a confirmed diagnosis of MS [30] (any duration or type), able to travel to one of the two research sites and self-reported UL impairment which interfered with ADLs, which was confirmed objectively by a Nine Hole Peg Test (NHPT) of 2 standard deviations or more above the published normative values [31].

Participants were excluded if they had: (1) a relapse in the last three months; (2) cognitive problems, such that they would be unable to use the VR equipment, (3) visual problems such that they could not see the visual display within the headset (wearing glasses was allowed); (4) current eye infection; (5) any

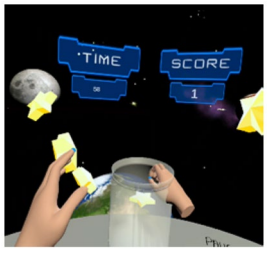
significant co-existing conditions affecting the ULs; (6) unable to understand English; (7) currently enrolled in other clinical trials.

Participants were recruited from MS clinics in NHS Lanarkshire and third sector organisations, e.g., MS Society Research Network and Revive MS Support. Potential participants within NHS Lanarkshire were identified by their practitioners and, if they were interested in participating, their contact information was shared with the lead investigator (AW). Participant information sheets were also left within the café at Revive MS Support and an electronic copy was distributed by the MS Society to their research network. Written informed consent was obtained from all participants. Participants were randomised by concealed allocation using opaque sealed envelopes (1:1 allocation ratio), prepared by a researcher out with the research team, indicating assignment to the intervention or control group [32,33]. The therapists, assessor and participants were not blind to the group allocation.

Intervention group

The intervention group received individual, supervised, UL rehabilitation using VR, lasting 30 min, twice per week for 8 weeks which was in line with prior research [26,34,35]. The VR involved up to three games; "Catch-a-Falling Star", "Whack-a-mole" and "Piano Game" (Table 1). Participants were prescribed games by their current therapist or by a therapist within the research team (LP, EC, KB) to focus on for their individual UL goals. The games, time of play and level of difficulty were therefore personalised to each participant. The VR games were delivered using the Oculus Quest 2 headset, using the hand tracking feature for two games and hand controllers for one game (Whack-a-mole). These games were developed by the lead author (AW) following a co-production approach previously described [14]. For health and safety reasons participants completed their programme whilst seated. The number of repetitions performed by participants were recorded during each session. Repetitions

Table 1. Description of co-produced VR games.

Name of game	Description of game	Image	Targeted movements	Difficulty progression
Catch-a-Falling Star	The user has to grasp falling stars and move them individually to a jar. The user plays for an allocated time (60 s) and the score indicates how many stars were added to the jar.		Shoulder elevation and rotation (reaching); Grasp and release of hand	Three levels of difficulty. Increasing speed of stars and most difficult level included thinner stars
Whack-a-Mole	The user hits appearing moles by holding a controller that represents a hammer. There is an additional cognitive element with moles resulting in a penalty or additional points. The user will do this for an allocated time (60 s) and is provided with a score at the end.		Shoulder rotation; Elbow/wrist flexion and extension	Three levels of difficulty. Increasing speed of moles and penalty for incorrect hits at middle and hardest levels of difficulty.
Piano Game	The user follows indicators to hit certain piano keys to play a tune. This can be done at different speeds depending on the user's preference. The scoring system indicates how many keys they were able to hit within the allocated time. Following music notes adds a cognitive element to the gameplay.		Wrist extension, finger flexion and extension; finger abduction.	Difficulty was represented by two different speeds of play and two different thickness of keys.

were documented during the session by recording the score which reflected successful actions and manually recorded any additional movements, such as missed actions, e.g., missing a star, mole or key. The Oculus Quest 2 headset required casting to another device (i.e., smartphone or tablet) to visualise the participant's performance. If any participants at any point tested positive for COVID-19 or had other illnesses during the intervention period, the intervention was paused and resumed following recovery.

Control group

The control group received usual care, meaning participants were advised to continue any current physiotherapy/exercise prescribed before the study and were not prescribed any additional physiotherapy through the trial. After the final assessment (week 8) a 30-min session of the VR games was offered. For both groups any ongoing physiotherapy or occupational therapy was recorded detailing the rehabilitation.

Data collection

The lead investigator (AW) was involved in the data collection of feasibility and clinical outcomes, and two co-authors were involved in the interview data collection (LP and EC). AW has a life science and technology background and was trained by clinicians on how to perform the clinical outcome measures. LP and EC are physiotherapists.

The following demographic information was collected: age, sex, MS type, time since diagnosis (TSD), highest level of education, occupation, level of disability by Patient Determined Disease Steps (PDDS) [36,37] and medications.

Feasibility outcomes

Feasibility outcomes were addressed by:

- Recruitment rates: number of participants that met eligibility criteria, number identified and approached; number excluded and reasons for exclusion; number that agreed to take part in the study; if participants accepted being randomised to the control arm
- Completion of intervention/drop-out rates from both groups and reason for drop-out or not completion
- Intervention adherence: the number of completed VR sessions and duration of these sessions, if the participants were able to complete the full session
- Time to set up the equipment and launch the application
- Completion of the outcome measures: baseline scores, distributional properties, and assessment of the suitability of outcomes for any future study
- Safety: adverse events (AE), especially those that may be related to the VR intervention
- Determining the sample size for a fully powered randomised controlled trial (RCT)

Clinical outcomes

The following clinical outcome measures were taken at baseline, week 4 (mid-point); and week 8 (end of intervention). Outcomes measures were conducted in the same order each time. The participants were offered a break between outcome measures if required.

The NHPT assesses the time taken to place nine pegs from a well into a pegboard, one at a time, and returned. Measurements were taken for both hands (non-dominant hand (NDH) and dominant hand (DH)). If a participant was unable to complete the NHPT, a score of 300s was assigned [38]. The NHPT is a reliable (intraclass correlation coefficient (ICC) = 0.947 (NDH); 0.937 (DH)) [39] and validated test in MS [38].

Hand grip strength was used as a proxy measure of general muscle strength [40]. Participants gripped the dynamometer (Jamar) as hard as possible for three seconds. The average of three maximal readings was recorded with a ten second rest between recordings for both NDH and DH. This test also has excellent reliability within MS (ICC = 0.98 (right hand); 0.98 (left hand)) [41].

The Action Research Arm Test (ARAT) involves 19 different items scored on a four-point ordinal scale from 0 (no movement) to 3 (normal). The score ranges between 0 and 57 for each hand, with higher scores indicating greater UL functional ability. Each category has its own score with Grasp (0–18); Grip (0–12); Pinch (0–18); Gross (0–9) [42]. The ARAT is another valid (Spearman's rho = 0.951) and reliable (ICC = 0.998) test within neurological populations such as MS [42].

The ABILHAND questionnaire allows participants to rate their ability to perform 23 daily living tasks without assistance using a three-point ordinal scale, 0 = impossible, 1 = difficult and 2 = easy [43]. The questionnaire has a maximum score of 46 with lower scores corresponding to poorer perceived functional ability. This score can then be converted to an interval measurement of logits by Rasch analysis, ranging from −6.078 to 6.017, again with the lower score representing lower functional ability [44]. The ABILHAND has both excellent reliability (Person Separation Index (PSI) = 0.95) and validity (r=-0.75) within MS [45].

The Spasticity-related quality of life (SQoL-6D) questionnaire has six domains: 1) pain/discomfort; 2) involuntary movements or spasms; 3) restricted range of movement; 4) caring for the affected limb(s); 5) using the affected limb(s); 6) interference of UL spasticity on mobility/balance [46]. It is scored from 0 to 100 such that higher scores relate to higher quality of life. There is a lack of data on the psychometric properties of Spasticity measures in MS. However, the SQoL-6D has good reliability (ICC = 0.82) and is quick and easy to administer [47].

Usability outcome

The Usability, Satisfaction and Ease of Use (USE) questionnaire (intervention group only, week 8) has four dimensions: usefulness, satisfaction, ease of use, and ease of learning [48]. The 30 statements are completed on a 7-point Likert scale (1: strongly disagree to 7: strongly agree).

Semi-structured interviews

A purposive sample of five participants from the intervention group participated in semi-structured interviews lasting approximately 30–45 min [49]. The interviews explored the acceptability of the intervention, any issues encountered and suggested improvements for future studies using the VR games. The interviews were conducted by either EC or LP *via* Microsoft Teams video call or phone call and audio recorded. Interviews were transcribed verbatim by AW.

Analysis

Statistical analysis was guided by the CONSORT 2010 statement: extension to randomised pilot and feasibility trials guidelines [50]. Data were analysed using intention-to-treat analysis with IBM Statistical Package for the Social Sciences (SPSS) v28. Due to the small sample size, non-parametric tests and descriptive analysis were used. Between group differences for demographic data were analysed by Mann Whitney U Test, Fisher's Exact Test and Pearson Chi-Square test, where appropriate. Between group differences for the clinical outcomes were analysed by using Mann Whitney U test, and Median confidence intervals (Hodges-Lehman Median Difference, 95%). Within group effect sizes (Cohen's d and correlation co-efficient using Wilcoxon signed rank test) were also calculated. Statistical significance was taken at $p < 0.05$ and effect sizes were classified as small (≤0.2), moderate (≤0.5), or large (≤0.8) [51].

Semi-structured interviews were analysed using thematic analysis following the six-step method as described by Braun and Clarke [52]. The transcripts were imported into NVivo qualitative analysis software, where codes were assigned and grouped into subthemes and then main themes. Codes and

themes were identified using an inductive, data driven approach. Pseudonyms were assigned alongside participants' quotes.

Results

Recruitment

Forty-nine pwMS were screened for eligibility from July 2022 to December 2022, with 19 participants recruited (Figure 1) and the trial finished due to time restrictions (April 2023). The recruitment period lasted six months, thus the recruitment rate was 3.2 participants per month. The most common reasons for exclusion at screening stage or not participating were no perceived UL problems ($n=6$), travel difficulties ($n=4$) and work commitments ($n=4$). Of the 19 participants enrolled, two dropped out, both in the control group, one due to scheduling difficulties and one due to a suspected relapse (Figure 1). All participants who were randomised to the control group accepted their group allocation.

Demographic data

Of the 19 participants enrolled: eleven were randomised to the intervention group and eight the control (Table 2). The mean age was 52.7 [±11] years, 68% of participants were female and the mean time since diagnosis was 17.1 [±9.1] years. There were varying MS types; secondary progressive MS (SPMS) (53%),

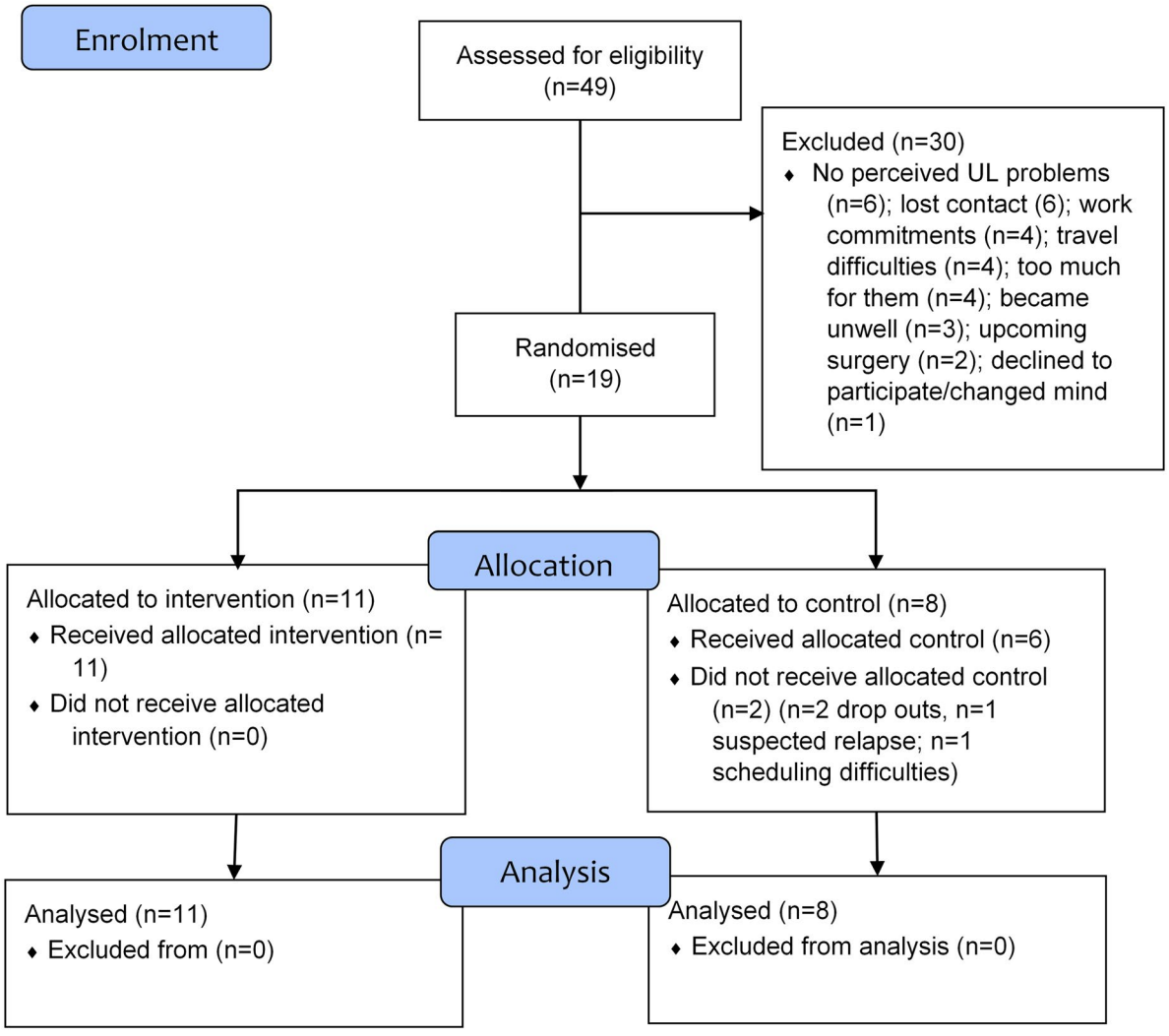


Figure 1. CONSORT flow diagram.

Table 2. Demographic data.

	Intervention ($n=11$)	Control ($n=8$)	Total ($n=19$)	Significance (p value)
Age (years) (mean [±SD])	51.2 [±12.9]	54.8 [±8.3]	52.7 [±11.0]	0.562[a]
Sex (%)				1.000[b]
Male	4 (36%)	2 (25%)	6 (32%)	
Female	7 (64%)	6 (75%)	13 (68%)	
MS Type (%)				0.659[c]
RRMS	5 (46%)	2 (25%)	7 (37%)	
PPMS	1 (9%)	1 (13%)	2 (11%)	
SPMS	5 (46%)	5 (63%)	10 (53%)	
TSD (years) (mean [±SD])	17.0 [±11.2]	17.1 [±5.9]	17.1 [±9.1]	0.483[a]
Highest stage of education				0.274[c]
No formal education	0	1 (13%)	1 (5%)	
High school	3 (27%)	1 (13%)	4 (21%)	
College	5 (46%)	1 (13%)	6 (32%)	
University undergraduate	0	1 (13%)	1 (5%)	
Doctorate	0	1 (13%)	1 (5%)	
Other (e.g., professional degree)	3 (27%)	3 (38%)	6 (32%)	
Occupation (%)				0.532[c]
Off work	1 (9%)	0	1 (5%)	
Unemployed	2 (18%)	1 (13%)	3 (16%)	
Retired/medically retired	8 (73%)	6 (75%)	14 (74%)	
Part-time	0	1 (13%)	1 (5%)	
PDDS (mean [±SD])	6 [±1.1]	5.5 [±1.5]	5.7 [±1.3]	0.464[a]
Current physiotherapy (%)				0.177[b]
Yes	5 (46%)	1 (13%)	6 (32%)	
No	6 (55%)	7 (88%)	13 (68%)	

Abbreviations: PDDS patient determined disease steps; PPMS primary progressive MS; RRMS relapse and remitting MS; SPMS secondary progressive MS; TSD time since diagnosis.
[a]Mann Whitney U.
[b]Fisher's Exact Test.
[c]Pearson Chi-Square.

Table 3. Number of repetitions for each participant per session and mean number of repetitions.

	Session number																
Participant ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Mean repetitions
VR01	285	477	1282	1232	1446	1969	1446	1519	1760	1633	1686	1587	1721	1459	1422	1515	1402
VR02	200	532	276	–	736	479	705	421	553	480	577	485	444	393	631	485	493
VR03	275	727	807	609	790	710	749	–	415	906	688	904	912	753	1088	632	731
VR04	350	531	527	728	868	789	909	813	1038	967	1175	947	990	–	976	857	831
VR05	282	449	490	580	828	762	–	752	796	990	835	754	813	1296	1097	1067	786
VR06	71	–	322	529	399	–	331	778	83	431	117	–	–	–	442	41	322
VR07	1011	714	–	838	520	866	788	990	861	973	469	1089	926	1035	757	833	845
VR08	775	1197	1213	1720	2617	–	1875	1579	2339	1847	1807	1533	2319	2312	2736	2371	1883
VR09	1402	980	1435	1762	1985	1316	–	1952	1086	650	1647	1926	2087	2294	–	1594	1580
VR10	1779	3152	3679	–	4025	2554	–	2709	2457	3309	–	2498	3243	–	3131	4191	3061
VR11	757	608	878	930	898	–	1124	1099	–	–	–	–	1338	–	1291	1080	1000
													Total mean repetitions [±SD]				1176 [±779]

Key: - missed session.

relapse and remitting MS (RRMS) (37%), and primary progressive MS (PPMS) (11%). Five participants (26%) were on disease modifying therapies. Only two participants (11%), both in the intervention group, were receiving physiotherapy involving their ULs. Only one participant was in paid employment and that was on a part-time basis (Table 2). There were no significant differences between groups for any demographic variables at baseline (Table 2).

Adherence and duration of sessions

Adherence to the intervention was generally high with a mean session completion rate of 87% [±12%]. The most common reason for missing sessions being illness/MS symptoms ($n=15$). In terms of session duration, most participants completed 30 min of exercise however 22 sessions (14%), involving four participants, had shorter sessions ranging from 2 to 23 min generally due to pre-existing fatigue ($n=10$). Most participants (64%) completed the intervention within the eight weeks. There were four participants that paused their intervention due to COVID-19 ($n=2$; 18%) or other illness ($n=2$; 18%). The mean number of

repetitions/movements per session was 1176 [±779] and generally increased over the intervention period (Table 3). The Whack-a-mole game typically provided more repetitions compared to the other games.

Technical issues

The equipment set up took approximately five minutes, between turning on the headset and the participant launching the games within the headset. Casting the HMD to the tablet for observation of the participants' gameplay required a good, stable internet connection which was not always possible depending on the mobile data/signal. There were also some hand tracking issues in five sessions caused by direct sunlight. Hand tattoos also affected the hand tracking system, which was rectified by wearing nitrile gloves.

Adverse events

Nine AEs, potentially related to the intervention were recorded: increased fatigue ($n = 3$); arm pain ($n = 2$); scapula pain ($n = 2$); eye strain ($n = 1$); and controlled falling to the floor ($n = 1$). The latter occurring when they lost their balance within their wheelchair whilst playing VR. The AEs associated with pain or discomfort typically occurred in the first session and generally improved over the eight weeks. No cybersickness or associated symptoms (e.g., dizziness, nausea) were reported. There was one serious AE, a hospitalisation unrelated to the study.

Outcome measures

Completion of outcome measures

All participants in the intervention group completed their outcome measures (baseline, week 4 and week 8) compared to 79% completion in the control group. The two ($n = 8$) participants who dropped out were unable to complete week 4 and week 8 assessments, with another participant missing week 4 assessments due to illness. All participants completed the outcomes within one week of the stated assessment date at week 4 and all but one at week 8.

Upper limb outcome measures

The intervention group showed mean improvements for all UL outcome measures at both timepoints compared to baseline, however, typically with small to moderate effect sizes (Table 4). There were also improvements in the control group in the NHPT (except NDH at week 4), ABILHAND and SQoL-6D, with small to moderate effect sizes (Table 4). The intervention group had greater mean improvements compared to the control group in the majority of outcome measures and timepoints, except NHPT DH at week 4. There was a mean decrease in handgrip strength within the control group compared to baseline for NDH week 4 and 8, DH week 8, again with small effect sizes. There was an observed ceiling effect within the ARAT with six and seven participants in VR and control groups respectively achieving the maximum score ($n = 57$) in at least one UL at baseline assessment. The majority of between group differences were not significant, except hand grip strength in NDH ($p = 0.003$; CI: 2.00–7.67) and DH ($p = 0.005$, CI: 1.67–8.00) at week 4, and DH ($p = 0.01$, CI: 2.33–8.33) at week 8 favouring the intervention group. There were no significant differences between groups at baseline for all UL outcome measures.

USE questionnaire

Overall, high usability ratings were obtained for the VR games. Of the four constructs in the USE questionnaire, the highest rated was ease of learning (6.57 [±0.8]), then satisfaction (6.45 [±1.2]), ease of use (6.17 [±1.5]) and usefulness (5.91 [±1.5]) (maximum score 7).

Table 4. Descriptive and non-parametric statistics for upper limb outcome measures.

Outcome measure	Intervention				Control				Difference between groups	
	N	Mean [SD]	Mean Change [SD] (CI, 95%)	Effect size (Cohen's *d*)	N	Mean [SD]	Mean Change [SD] (CI, 95%)	Effect size (Cohen's *d*)	Sig.	Median CI (95%)
NHPT (s)										
Baseline NDH	11	112.44 [121.30]			8	62.34 [29.23]			0.9	−37.81–217.9
Week 4 NDH	11	104.28 [125.87]	−8.16 [11.82] (−16.10 – −0.22)	0.07	5	74.26 [19.09]	4.13 [20.12] (−20.86–29.11)	0.46	0.18	−31.42–2.73
Week 8 NDH	11	103.00 [123.60]	−9.44 [11.96] (−17.47 – −1.49)	0.08	6	69.54 [10.42]	−2.59 [18.76] (−22.28–17.10)	0.31	0.26	−22.02–4.230
Baseline DH	11	45.27 [13.05]			8	45.18 [19.49]			0.66	−16.37–16.1
Week 4 DH	11	43.53 [23.49]	−1.74 [15.52] (−12.17–8.68)	0.1	5	50.02 [7.95]	−4.01 [13.87] (−21.24–13.21)	0.3	1.00	−15.33–16.96
Week 8 DH	11	40.84 [18.90]	−4.43 [13.18] (−13.29–4.43)	0.27	6	48.24 [9.95]	−2.96 [12.76] (−16.34–10.43)	0.19	0.59	−16.19–12.33
Hand grip strength. (kg)										
Baseline NDH	11	13.21 [7.11]			8	13.79 [6.26]			0.78	−8.00–6.33
Week 4 NDH	11	15.91 [7.60]	2.70 [2.38] (1.10–4.30)	0.37	5	14.27 [6.22]	−2.27 [2.53] (−5.41–0.88)	0.07	**0.003***	2.00–7.67
Week 8 NDH	11	16.30 [7.26]	3.09 [3.49] (0.74–5.43)	0.43	6	13.89 [5.04]	−2.28 [3.01] (−5.54–0.88)	0.02	**0.005***	1.67–8.00
Baseline DH	11	20.91 [7.12]			8	15.46 [7.43]			0.13	−1.33–13.33
Week 4 DH	11	23.12 [7.12]	2.21 [2.73] (0.38–4.05)	0.31	5	18.27 [8.95]	0.73 [3.52] (−3.64–5.11)	0.35	0.38	−2.00–5.33
Week 8 DH	11	23.73 [5.81]	2.82 [3.28] (0.62–5.02)	0.43	6	15.06 [5.32]	−2.67 [2.53] (−5.32 – −0.01)	0.06	**0.01***	2.33–8.33
ABILHAND (logits)										
Baseline	11	0.15 [1.06]			8	0.28 [0.95]			1.00	−1.15–0.98
Week 4	11	0.96 [1.08]	0.81 [0.95] (0.17–1.44)	0.76	5	0.29 [0.53]	0.25 [0.35] (−0.18–0.68)	0.01	0.28	−0.36–1.64
Week 8	11	1.09 [1.43]	0.94 [1.11] (0.20–1.68)	0.75	6	−0.07 [0.60]	−0.05 [0.33] (−0.53–0.35)	0.42	0.06	−0.03–2.19
SQoL-6D										
Baseline	11	65.14 [22.75]			8	70.22 [20.22]			0.6	−0.67–1.00
Week 4	11	72.36 [19.81]	7.23 [21.46] (−7.19–21.64)	0.34	5	78.35 [16.52]	5.15 [13.50] (−11.61–21.92)	0.43	0.91	−20.75–29.25
Week 8	11	71.23 [18.00]	6.09 [20.55] (−7.71–19.90)	0.3	6	79.08 [13.25]	2.13 [15.94] (−16.78–25.18)	0.5	0.81	−16.75–25.00
	N	Median [IQR]	Median Change [IQR]	Effect size (r)	N	Median	Median Change [IQR]	Effect size (r)	Sig.	Median CI
ARAT (Total)										
Baseline NDH	11	52.00 [48.00–57.00]			8	52.00 [49.25–57.00]			0.72	−8.0–5.0
Week 4 NDH	11	57.00 [54.00–57.00]	2.00 [0–5.00]	0.01	5	52.00 [47.50–56.50]	−2.00 [−4.00–5.00]	0.06	0.27	−4.00–7.00
Week 8 NDH	11	57.00 [54.00–57.00]	2.00 [0–5.00]	0.04	6	56.60 [50.75–57.00]	4.00 [1.50–6.00]	0.02	0.88	−4.00–4.00
Baseline DH	11	56.00 [51.00–57.00]			5	57.00 [51.75–57.00]			0.35	−0.5–5.0
Week 4 DH	11	57.00 [53.00–57.00]	1.00 [0–2.00]	0.03	6	56.00 [52.50–57.00]	0 [−0.50–3.00]	0.12	0.74	−2.00–2.00
Week 8 DH	11	57.00 [56.00–57.00]	1.00 [0–5.00]	0.01	8	56.60 [54.75–57.00]	0 [−0.25–5.00]	0.11	0.40	−2.00–4.00

Abbreviations: ARAT (Action Research Arm Test); CI (confidence interval); DH (dominant hand); IQR (interquartile range); kg (kilograms); N (number of participants); NDH (non-dominant hand); NHPT (nine-hole peg test); r (correlation co-efficient using Wilcoxon signed rank test); SD (standard deviation); Sig, significance ($p < 0.05$). Effect size is calculated as a comparison at baseline.
Mean, mean difference and confidence intervals are presented for NHPT, hang grip strength, ABILHAND, SQoL-6D; and median, median difference and confidence intervals presented for ARAT.

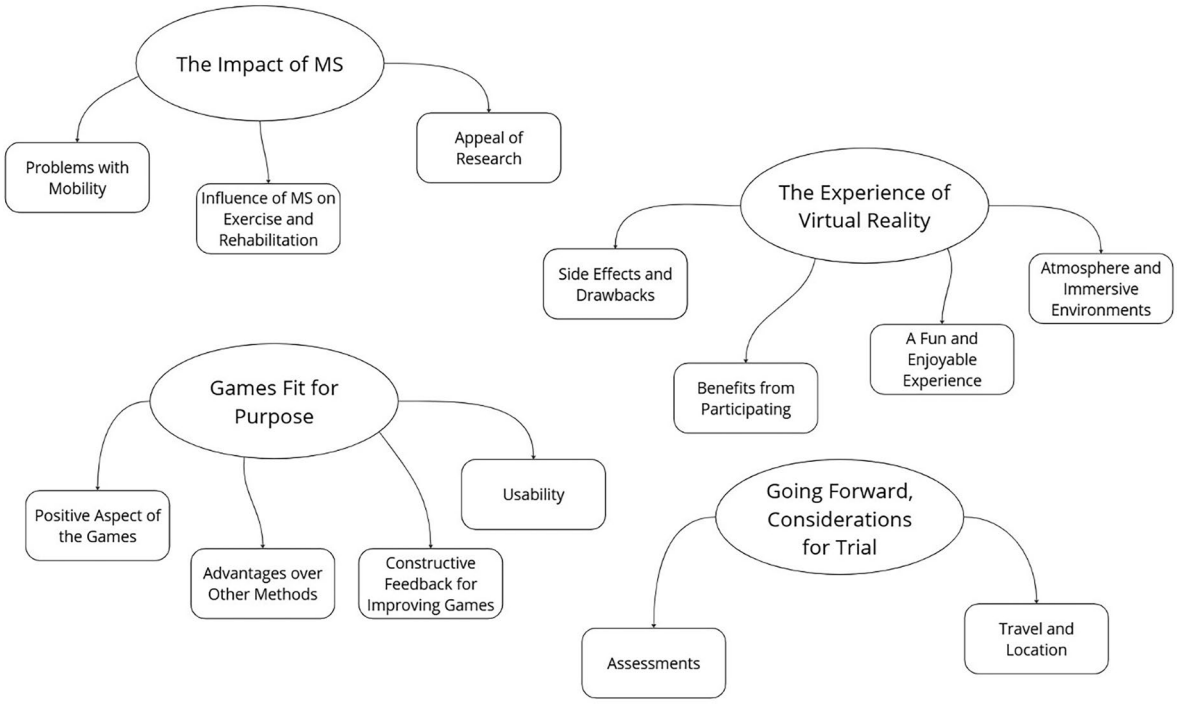


Figure 2. Theme map of the main and sub-themes emerged from thematic analysis from post-intervention interviews.

Semi-structured interviews

Five participants, consisting of 4 female and 1 male and mean age of 56 [±13.8] years, took part in the interviews. Four had SPMS, one had RRMS, and the mean TSD was 16 [±15] years.

Thematic analysis of the interview data resulted in four main themes and 13 sub-themes, (Figure 2). The four themes were (1) The Impact of MS; (2) The Experience of VR; (3) Games Fit for Purpose; and (4) Going Forward: Considerations for Trial Improvements. Quotes are provided below, with additional quotes provided in the Supplementary Table S1.

Theme 1: the impact of MS

Sub-theme: problems with mobility

There were varying degrees of UL problems experienced: reaching upwards, gripping and grasping, and fine finger movement. Loss of strength, joint stiffness and loss of sensation were also reported. The consequences of such UL problems were interference with sleep and everyday activities, such as chopping vegetables, carrying items, and fastening buttons and zips. Participants often adapted how they would perform tasks however noted the effort involved. Participants appreciated that it was meaningful to keep or regain their arm function, for activities such as pressure relief or using walking aids.

Sub-theme: influence of MS on exercise and rehabilitation

Having MS had a negative impact on the ability to exercise, but participants also described exercise being important for them and that maintaining function was a more realistic rehabilitation goal than improvement. Participants had different experiences specifically with UL rehabilitation, from never receiving UL rehabilitation to one participant undergoing intense rehabilitation.

Sub-theme: appeal of research

Participants agreed to take part in the study hoping it would be helpful for them and to use their experience of having MS for the greater good.

"I thought that it would be good for my arms and things like that and MS. I'll try any study on MS" Lynn (age 60, SPMS)

Theme 2: the experience of virtual reality

Sub-theme: a fun and enjoyable experience

All the participants interviewed expressed that the VR intervention was an enjoyable experience, describing it as "fun", "different" or "fantastic". They particularly enjoyed the Whack-a-mole game.

Sub-theme: atmosphere and immersive environments

Most participants were impressed and impacted with the different environments of the VR including the ambient background sounds contributing to the feeling of tranquillity.

"The first few times I was playing I was aware of other planets in the sky of satellites going around as a planet being there and I find absolutely incredible the stars the darkness… I was there I think … my third or fourth week, when I kind of leaned forward to it down and saw that actually, I was sitting on the outside of a rocket spaceship. And below me, was the earth going round… and I find it absolutely fascinating" Fiona (age 62, SPMS)

Participants also appreciated that the arcade machines in Whack-a-mole had names that were related to MS, such as MS Warrior and Myelin Hunt. Only one participant did not feel immersed in these environments but felt the background imagery was still a pleasant alternative to the real world.

Sub-theme: benefits from participating

The majority of participants interviewed believed that the study had improved their UL function to varying degrees. Improvements in range and speed of movement, strength, dexterity, and reduced stiffness in the hands translated into improvements in tasks such as changing the bedsheets, getting dressed and reaching up into cupboards.

"I'll have [the study] to thank for this that I got there – weeks and weeks of working on reaching and a bit of stability in this side… I celebrated the day that I was able to carry 2 glasses from the kitchen into the living room, so that me and my other half could both have a drink at the same time." Jane (age 34, RRMS)

As well as physical benefits participants highlighted psychological benefits from the intervention being relaxing (Catch-a-falling star) to working out aggression/stress (Whack-a-mole). One participant had no notable improvements, but felt overall it was beneficial. Participants expressed enjoyment in taking part in the VR research, all participants stated they would recommend it due to the benefits they had experienced.

Sub-theme: side effects and drawbacks

The majority of participants had no side-effects from taking partaking in VR while some reported increased fatigue. However, this side effect tended to improve over the course of the study. One participant also found the VR game increased her neck pain temporarily. Other issues raised were the weight of the VR headset, fogging of their glasses and lenses within headset.

Theme 3: games fit for purpose

Sub-theme: advantages over other methods

The majority of participants described how the VR games were more "fun" than typical physiotherapy which could be "dull". VR was appealing, invoked intrigue and eliminated the feeling of exercise being a chore. Participants felt the VR games motivated them to work harder and could perhaps be useful for those less keen to exercise.

"You're totally engrossed, you're focused on the task… there's an aim that you've got to get them all… Certainly going to virtual reality was a lot easier than getting ready to go to a gym, or lay all my equipment out in the

house… lay my yoga mat down, and then I'll lay down and then I'll lay there and I'll think well, what will I do?" Erin (age 56, SPMS)

Sub-theme: positive aspects of the games

The different games offering different movements of the UL and trunk allowed participants to focus on their rehabilitation targets was seen as positive. The timer and the different levels of difficulty were motivating and encouraged participants to work harder. In addition, the visual scoring systems introduced a competitive element and beating personal best scores felt like an achievement.

Sub-theme: usability

Overall participants described the use of the VR as "easy". However, one participant experienced difficulty grasping the controller with her weakened hand. Even those who referred to themselves as "slow learners" learned how to use VR over the course of the intervention.

Sub-theme: constructive feedback for improving games

Most of the game feedback for improvement was regarding the piano game which was described as initially difficult, not as exciting as the other games and periodically had issues with the finger tracking. Suggestions for improvement were increasing the variety of games for longer term engagement and to incorporate more progression, especially for those with less disability.

"Although there was a grading in like one, two and three levels, there was no specific sort of like moving on, once you achieved a certain level. So, you know, for example… I was able to do grade three right from day one. So there was no next level up" Erin (age 56, SPMS)

Theme 4: going forward, considerations for trial improvements

Sub-theme: assessments

There were conflicting opinions about the suitability of the assessments used in the study being representative of their disability and priorities. The assessment length was acceptable, although tiring for some, and did not capture the daily variability often experienced by pwMS.

Sub-theme: travel and location

Participants came to the research site by car, taxi or bus. While there were some issues with taxis not arriving, some enjoyed being "out and about". There were varying opinions regarding clinic versus home use; concern that people could do too much at home and others preferring to get out of the house. Generally, the clinic was felt to be more motivating and offered supervision which was seen as very valuable.

"I really liked the structure and motivation from the appointment. A set routine makes you do the exercise and I don't think I would have worked as hard at home. I liked the encouragement" Alexander (age 71, SPMS)

Discussion

This study aimed to investigate the feasibility of an eight-week RCT intervention of co-produced immersive VR games for UL rehabilitation for pwMS, using a mixed methods design. Data from the feasibility outcome measures and the participant interviews, demonstrated the supervised VR intervention was a feasible, acceptable and safe method for delivering UL rehabilitation for pwMS.

Recruitment

The study failed to reach the recruitment target of 30 participants, with recruitment rates of 3.2 participants/month. In addition, 61% of potential participants screened for eligibility declined or were not

eligible to take part. Recruitment challenges are not uncommon for physical rehabilitation studies involving pwMS, due to resource restrictions, such as time and staff, and the condition itself being a barrier for people to participate [53]. In this present study, one of the most common reasons for exclusion was no perceived UL problems. UL dysfunction is more prevalent within progressive MS, and in turn more disabled individuals, who can face barriers to exercise and challenges for participation in research [54,55].

The demanding nature of the trial and travel difficulties were other common given reasons for not participating, which have been similarly reported in other MS rehabilitation trials [56,57]. To accommodate those with greater disability or individuals unable to travel, a home-based approach could be adopted in future studies. However, this would require additional considerations, such as safety; training; monitoring adherence and performance; and particularly for bespoke interventions, equipment use and maintenance [58]. Home-based approaches for this type of intervention within MS have been previously explored, but feasibility and evaluation data are very limited [27]. It is also worth noting that participants interviewed believed that there were benefits to in-person intervention, such as motivation and supervision, which should be considerations for home-based approaches using VR in future. Highlighting the importance of refining the recruitment method to increase recruitment rates to ensure feasibility of this type of intervention study in future research, such as adding more recruitment sites.

Drop outs

This study had two participants drop out, both in the control group (11%). This figure is on the low end of the range of drop outs from our previous review, which ranged from 0%-38% [26]. Although these dropouts were in the control group, the control group accepted their random group allocation, and dropped out for unrelated reasons (time constraints and suspected relapse).

Adherence

There was good adherence to the highly immersive VR intervention within this study (87 ± 12%). This is in line with the adherence previously reported to both low and high immersive VR, reported within UL rehabilitation studies in MS, ranging from 82% to 100% session completion [26,59].

Overall, whilst there are some challenges in terms of recruitment to the study, when participants were recruited the retention within the study and adherence to the VR intervention were good. Although to improve recruitment in future studies the feasibility of a home-based VR intervention should be explored.

Safety

This study demonstrated that the immersive VR intervention, involving three bespoke games, was safe for pwMS, in supervised sessions. While there were a small number of AEs ($n = 9$), there was no self-reported cybersickness, which is an encouraging finding. To date, there has been inadequate information available regarding safety of immersive VR physical rehabilitation since only a small number of studies have been published with limited reporting of AEs [26,60]. In a recent study investigating feasibility of two bespoke games using the previous Oculus HMD, the Oculus Rift, some participants reported fatigue, dizziness, and nausea to varying degrees after a single session [61]. It is not clear why there were differences in cybersickness-related AEs between Kalron et al. [61] and the current study, but could be due to participants' standing during VR gameplay. Standing during gameplay, particularly involving movement, is more likely to invoke cyber-sickness compared to sitting [62]. Therefore, seated play, which does not negatively impact player satisfaction [63] should be recommended for individuals more susceptible to motion sickness. One participant in the present study had a controlled fall to the floor, thus individuals with poorer stability should avoid excessive movement, such as reaching too far, to prevent injury or falling out of their chair/wheelchair during VR gameplay [64].

Experience and acceptability of VR

The user experience and acceptability of VR were determined through integrating the results from the USE questionnaire and interviews. The VR intervention was praised highly by participants in terms of usability and satisfaction. To our knowledge this is the first study to gather qualitative data on the experience of immersive VR for pwMS.

The experience of the VR intervention was positive for participants, reflected by high mean scores in all domains of the USE questionnaire and themes raised from the interviews often reflecting enjoyment and the self-perceived benefits, in particular praising the VR intervention for its distraction, encouragement of exercise and advantages over traditional exercise.

There is a lack of previous research regarding the experience of VR UL rehabilitation for pwMS. However, a previous study that used a non-validated questionnaire to assess the satisfaction and engagement of a home-based intervention using the Oculus Quest 2, similarly reported that pwMS found VR fun and would recommend it to other pwMS [27]. Participants also suggested improvements to the VR activities, such as adding difficulty levels and scores [27], which were elements incorporated into the design of the games within the present study. However, there was feedback in the current study, from both the USE questionnaire and interviews, that future development of the games should include an increase in number and levels of difficulty, to offer more variety and progression, which is important for long-term use.

Self-competition and being able to beat previous scores were highly motivating for participants within the current study. The ability to visualise scores is a common motivational factor, adding an element of challenge for players in the general population [65]. However, Matin and colleagues [65] also found some participants experienced frustration when high scores were not achieved, therefore supporting offering personal preference settings in game design.

The participants believed the VR games were fit for purpose, with participants appreciating the design of the games, encouraging movement within the games and navigation through the application. Usability was also rated highly, in terms of ease of use and learning how to use the application. This highlights the benefits of co-produced, customisable, bespoke applications and supports conclusions of previous studies that specifically tailored games are more suitable to the intended user population [59,66]. Kamm and colleagues [27] reported high usability scores for their bespoke VR activities for pwMS, and recommended training sessions, detailed instructions and having usability as the forefront of their design. Whereas Bertoni et al. [67] had a lower usability score when using the Oculus Rift and commercial exergames, with participants suggesting they were not user friendly. This reinforces the importance of more accessible/bespoke games for people with reduced mobility.

UL outcome measures

There were trends towards positive outcomes after the intervention in both objective and patient-reported outcome measures although the study was underpowered to determine effectiveness.

The improvements in hand grip strength were greater in the intervention group compared to the control, in both NDH at week 4 and 8 and DH at week 8. This is similar to previous research using non-immersive VR, which reported within group significant improvements in hand grip strength with a similar dose of VR to the current study [68]. The effect of VR interventions on other UL outcome measures, such as NHPT, are inconsistent within research. In this present study, the VR group typically have greater mean improvements in the NHPT compared to control. Significant improvements in NHPT have been found after a 4-week intervention using Kinect [69,70] and non-significant improvements in both NHPT and hand grip strength were reported after four weeks of an immersive VR intervention [67], with all studies being underpowered. Therefore, future studies should include larger sample sizes that are adequately powered to determine the effectiveness of VR interventions for UL rehabilitation in MS.

The outcome measures were acceptable to those interviewed and furthermore the positive changes in the objective outcome measures were supported by participants who also reported examples of improvements in their UL function post intervention.

The ARAT was not suitable for this population due to the ceiling effect present within the results. The ARAT may be more applicable to more disabled individuals, and within this study there was a range in level of disability [71]. Therefore, any future trials may consider other outcomes such as box and blocks test or kinematic analysis measures to test upper limb function.

In terms of estimating the sample size for any future RCT, using the data from the NHPT, which has been proposed as the primary outcome measure due to its good psychometric properties [38], it is estimated that the difference between groups for the NDH at week 8, would be 6.85s, assuming a standard deviation of 14.51s. Therefore, for 80% power at a 0.05 significance level, 71 participants per group (142 total) would be required for statistical significance for a future fully powered trial [72].

Allowing for a potential 15% dropout rate, a future RCT would then require 82 participants to be recruited per group. Regarding the number of potential participants who would need to be approached to achieve the recruitment rates required, this is challenging to calculate due to the lack of data from the NHS recruitment site in the current study. From the eligibility screening, 30 out of 49 participants were excluded or declined to participate (61%). Therefore, using an exclusion rate of 70%, 279 pwMS would need to be screened for eligibility to recruit 82 participants per group.

For the dosage of the intervention, this study's protocol was an 8-week intervention, similar to other VR interventions for the UL in MS [73–75]. However, the duration of the sessions and thus overall dosage vary, with other protocols ranging from one 45-min session/week [73] to two 50-min sessions/week [75]. To date there is insufficient evidence to determine the optimal dosage of VR intervention for UL rehabilitation.

Strengths and limitations

To our knowledge, this study is the first to investigate the feasibility of an RCT which used co-produced immersive VR games as its intervention, as well as using a mixed method approach providing both quantitative and qualitative feasibility data. In terms of limitations, the recruitment target was not met and thus a smaller than anticipated sample size was achieved. There were only two drop outs and one participant from the control group missed their week 4 assessment. Otherwise there was little missing data. It was also not possible to have a blind assessor which increases the potential risk of detection bias. There were also no long-term follow up and therefore it is unclear if the improvements were sustained after the intervention. The study was also underpowered; therefore, UL outcome measure results should be interpreted with caution.

The VR games software was bespoke and designed specifically for the MS population [14]. Future research should investigate cost-effectiveness as well as clinical effectiveness of VR and commercialisation of the software to ensure accessibility to those who could benefit.

There were only three games within the suite, offering a limited variety to participants. There were some technical difficulties, e.g., tattoos affecting the hand tracking of the Oculus, but these were easily rectified. Finally, the quantity of movement but not the quality of movement was recorded and future work should aim to record both quantity and quality.

Conclusion

This study is the first randomised, controlled feasibility study to investigate an intervention of immersive VR involving co-produced games for UL rehabilitation for pwMS. Overall, immersive VR appears to be a promising UL intervention for pwMS. The findings suggest the intervention is feasible, safe and acceptable for pwMS, with participants commenting positively on its usability, the atmosphere, fun and enjoyment elements, as well as the distracting and immersive environments. Overall suggesting VR provided a more positive experience than traditional forms of rehabilitation. Participants reported benefits from participating and there were positive trends within the UL outcome measures. These findings support a future RCT which would require a recruitment target of 164 participants (allowing for a 15% dropout rate) with a larger suite of games and an alternative to the ARAT as the primary outcome measure.

Acknowledgements

The authors wish to give our sincerest thanks to all people with MS who took part in this study. We also give thanks to the staff at NHS Lanarkshire and MS Revive Support, for their help with recruitment.

Author contributions

CRediT: **Amy Webster**: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Writing – original draft, Writing – review & editing; **Matthieu Poyade**: Conceptualization, Funding acquisition, Methodology, Software, Supervision, Writing – review & editing; **Elaine Coulter**: Conceptualization, Investigation, Methodology, Supervision, Writing – review & editing; **Niall John James MacDougall**: Investigation, Resources, Writing – review & editing; **Karen Brown**: Resources, Writing – review & editing; **Lorna Paul**: Conceptualization, Funding acquisition, Investigation, Methodology, Supervision, Writing – review & editing.

Disclosure statement

The authors report no conflicts of interest.

Funding

This work was supported by the Multiple Sclerosis (MS) Society, UK (under grant number 115). Multiple Sclerosis Society is a registered charity in England & Wales number 1139257 and in Scotland registered charity number SC041990.

References

[1] Walton C, King R, Rechtman L, et al. Rising prevalence of multiple sclerosis worldwide: insights from the Atlas of MS, third edition. Mult Scler. 2020;26(14):1816–1821. doi: 10.1177/1352458520970841.
[2] Rommer PS, Eichstädt K, Ellenberger D, et al. Symptomatology and symptomatic treatment in multiple sclerosis: results from a nationwide MS registry. Mult Scler. 2019;25(12):1641–1652. doi: 10.1177/1352458518799580.
[3] Ovacik U, Tarakci E, Ozdemir Z. Upper limb dysfunction in people with early-stage multiple sclerosis: perceived performance can be misleading. Mult Scler Relat Disord. 2023;79:104944. doi: 10.1016/j.msard.2023.104944.
[4] Bertoni R, Lamers I, Chen CC, et al. Unilateral and bilateral upper limb dysfunction at body functions, activity and participation levels in people with multiple sclerosis. Mult Scler. 2015;21(12):1566–1574. doi: 10.1177/1352458514567553.
[5] Marrie RA, Cutter GR, Tyry T, et al. Upper limb impairment is associated with use of assistive devices and unemployment in multiple sclerosis. Mult Scler Relat Disord. 2017;13:87–92. doi: 10.1016/j.msard.2017.02.013.
[6] Newsome SD, von Geldern G, Shou H, et al. Longitudinal assessment of hand function in individuals with multiple sclerosis. Mult Scler Relat Disord. 2019;32:107–113. doi: 10.1016/j.msard.2019.04.035.
[7] Cattaneo D, Lamers I, Bertoni R, et al. Participation restriction in people with multiple sclerosis: prevalence and correlations with cognitive, walking, balance, and upper limb impairments. Arch Phys Med Rehabil. 2017;98(7):1308–1315. doi: 10.1016/j.apmr.2017.02.015.
[8] Bass AD, Van Wijmeersch B, Mayer L, et al. Effect of multiple sclerosis on daily activities, emotional well-being, and relationships. Int J MS Care. 2020;22(4):158–164. doi: 10.7224/1537-2073.2018-087.
[9] Alonso RN, Eizaguirre MB, Cohen L, et al. Upper limb dexterity in patients with multiple sclerosis. Int J MS Care. 2021;23(2):79–84. doi: 10.7224/1537-2073.2019-083.
[10] Koch MW, Murray TJ, Fisk J, et al. Hand dexterity and direct disease related cost in multiple sclerosis. J Neurol Sci. 2014;341(1–2):51–54. doi: 10.1016/j.jns.2014.03.047.
[11] Spooren AI, Timmermans AA, Seelen HA. Motor training programs of arm and hand in patients with MS according to different levels of the ICF: a systematic review. BMC Neurol. 2012;12(1):49. doi: 10.1186/1471-2377-12-49.
[12] Lamers I, Maris A, Severijns D, et al. Upper limb rehabilitation in people with multiple sclerosis: a systematic review. Neurorehabil Neural Repair. 2016;30(8):773–793. doi: 10.1177/1545968315624785.
[13] Lamers I, Raats J, Spaas J, et al. Intensity-dependent clinical effects of an individualized technology-supported task-oriented upper limb training program in multiple sclerosis: a pilot randomized controlled trial. Mult Scler Relat Disord. 2019;34:119–127. doi: 10.1016/j.msard.2019.06.014.
[14] Webster A, Poyade M, Coulter E, et al. Views of specialist clinicians and people with multiple sclerosis on upper limb impairment and the potential role of virtual reality in the rehabilitation of the upper limb in multiple sclerosis: focus group study. JMIR Serious Games. 2024;12(1):e51508. doi: 10.2196/51508.
[15] Burks JS, Bigley GK, Hill HH. Rehabilitation challenges in multiple sclerosis. Ann Indian Acad Neurol. 2009;12(4):296–306. doi: 10.4103/0972-2327.58273.

[16] Wohlgenannt I, Simons A, Stieglitz S. Virtual reality. Bus Inf Syst Eng. 2020;62(5):455–461. doi: 10.1007/s12599-020-00658-9.
[17] Tuah NM, Ahmedy F, Gani A, et al. A survey on gamification for health rehabilitation care: applications, opportunities, and open challenges. Information. 2021;12(2):91. doi: 10.3390/info12020091.
[18] Siricharoen W. The effect of virtual reality as a form of escapism. CONF-IRM 2019 Proceedings; 2019. p. 36.
[19] Hamad A, Jia B. How virtual reality technology has changed our lives: an overview of the current and potential applications and limitations. Int J Environ Res Public Health. 2022;19(18):11278. doi: 10.3390/ijerph191811278.
[20] Lum HC, Greatbatch R, Waldfogle G, et al. How immersion, presence, emotion, & workload differ in virtual reality and traditional game mediums. Proc Human Factors Ergon Soc Ann Meet. 2018;62(1):1474–1478. doi: 10.1177/1541931218621334.
[21] Yao S, Kim G. The effects of immersion in a virtual reality game: presence and physical activity. In: Fang X, editor. HCI in games. Cham: Springer International Publishing; 2019. p. 234–242. doi: 10.1007/978-3-030-22602-2_18.
[22] Laver KE, Lange B, George S, et al. Virtual reality for stroke rehabilitation. Cochrane Database Syst Rev. 2025;6(6):CD008349. doi: 10.1002/14651858.CD008349.pub4.
[23] Chen J, Or CK, Chen T. Effectiveness of using virtual reality–supported exercise therapy for upper extremity motor rehabilitation in patients with stroke: systematic review and meta-analysis of randomized controlled trials. J Med Internet Res. 2022;24(6):e24111. doi: 10.2196/24111.
[24] Lei C, Sunzi K, Dai F, et al. Effects of virtual reality rehabilitation training on gait and balance in patients with Parkinson's disease: a systematic review. PLoS One. 2019;14(11):e0224819. doi: 10.1371/journal.pone.0224819.
[25] Schiza E, Matsangidou M, Neokleous K, et al. Virtual reality applications for neurological disease: a review. Front Robot AI. 2019;6:100.
[26] Webster A, Poyade M, Rooney S, et al. Upper limb rehabilitation interventions using virtual reality for people with multiple sclerosis: a systematic review. Mult Scler Relat Disord. 2021;47:102610. doi: 10.1016/j.msard.2020.102610.
[27] Kamm CP, Kueng R, Blättler R. Development of a new immersive virtual reality (VR) headset-based dexterity training for patients with multiple sclerosis: clinical and technical aspects. Technol Health Care. 2024;32(2):1067–1078. doi: 10.3233/THC-230541.
[28] Pau M, Porta M, Bertoni R, et al. Effect of immersive virtual reality training on hand-to-mouth task performance in people with multiple sclerosis: a quantitative kinematic study. Mult Scler Relat Disord. 2023;69:104455. Available from doi: 10.1016/j.msard.2022.104455.
[29] Skivington K, Matthews L, Simpson SA, et al. A new framework for developing and evaluating complex interventions: update of Medical Research Council guidance. BMJ. 2021;374:n2061. doi: 10.1136/bmj.n2061.
[30] Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018;17(2):162–173. doi: 10.1016/S1474-4422(17)30470-2.
[31] Oxford Grice K, Vogel KA, Le V, et al. Adult norms for a commercially available nine hole peg test for finger dexterity. Am J Occup Ther. 2003;57(5):570–573. doi: 10.5014/ajot.57.5.570.
[32] Halbert JA, Silagy CA, Finucane P, et al. Recruitment of older adults for a randomized, controlled trial of exercise advice in a general practice setting. J Am Geriatrics Soc. 1999;47(4):477–481. doi: 10.1111/j.1532-5415.1999.tb07242.x.
[33] Clark L, Dean A, Mitchell A, et al. Envelope use and reporting in randomised controlled trials: a guide for researchers. Res Meth Med Health Sci. 2021;2(1):2–11. doi: 10.1177/2632084320957204.
[34] Feys P, Coninx K, Kerkhofs L, et al. Robot-supported upper limb training in a virtual learning environment: a pilot randomized controlled trial in persons with MS. J Neuroeng Rehabil. 2015;12(1):60. doi: 10.1186/s12984-015-0043-3.
[35] Ortiz-Rubio A, Cabrera-Martos I, Rodríguez-Torres J, et al. Effects of a home-based upper limb training program in patients with multiple sclerosis: a randomized controlled trial. Arch Phys Med Rehabil. 2016;97(12):2027–2033. doi: 10.1016/j.apmr.2016.05.018.
[36] Hohol MJ, Orav EJ, Weiner HL. Disease steps in multiple sclerosis: a longitudinal study comparing disease steps and EDSS to evaluate disease progression. Mult Scler. 1999;5(5):349–354. doi: 10.1177/135245859900500508.
[37] Kister I, Bacon TE, Chamot E, et al. Natural history of multiple sclerosis symptoms. Int J MS Care. 2013;15(3):146–158. doi: 10.7224/1537-2073.2012-053.
[38] Feys P, Lamers I, Francis G, et al. The Nine-Hole Peg Test as a manual dexterity performance measure for multiple sclerosis. Mult Scler. 2017;23(5):711–720. doi: 10.1177/1352458517690824.
[39] Hervault M, Balto JM, Hubbard EA, et al. Reliability, precision, and clinically important change of the Nine-Hole Peg Test in individuals with multiple sclerosis. Int J Rehabil Res. 2017;40(1):91–93. doi: 10.1097/MRR.0000000000000209.
[40] Lamers I, Kelchtermans S, Baert I, et al. Upper limb assessment in multiple sclerosis: a systematic review of outcome measures and their psychometric properties. Arch Phys Med Rehabil. 2014;95(6):1184–1200. doi: 10.1016/j.apmr.2014.02.023.
[41] Paltamaa J, West H, Sarasoja T, et al. Reliability of physical functioning measures in ambulatory subjects with MS. Physiother Res Int. 2005;10(2):93–109. doi: 10.1002/pri.30.

[42] Platz T, Pinkowski C, van Wijck F, et al. Reliability and validity of arm function assessment with standardized guidelines for the Fugl-Meyer Test, Action Research Arm Test and Box and Block Test: a multicentre study. Clin Rehabil. 2005;19(4):404–411. doi: 10.1191/0269215505cr832oa.
[43] Penta M, Thonnard JL, Tesio L. ABILHAND: a Rasch-built measure of manual ability. Arch Phys Med Rehabil. 1998;79(9):1038–1042. doi: 10.1016/s0003-9993(98)90167-8.
[44] ABILHAND. Rehab-scales. [Internet]. [cited 2025 Dec 21]. Available from: https://www.rehab-scales.org/scale/abilhand.
[45] Barrett L, Cano S, Zajicek J, et al. Can the ABILHAND handle manual ability in MS? Mult Scler. 2013;19(6):806–815. doi: 10.1177/1352458512462919.
[46] Turner-Stokes L, Fheodoroff K, Jacinto J, et al. The spasticity-related quality of life 6-dimensions instrument in upper-limb spasticity: part I development and responsiveness. J Rehabil Med. 2022;54:jrm00244. doi: 10.2340/jrm.v53.690.
[47] Turner-Stokes L, Fheodoroff K, Jacinto J, et al. The spasticity-related quality of life 6-dimensions instrument in upper-limb spasticity: part II a first psychometric evaluation. J Rehabil Med. 2022;54:jrm00243. doi: 10.2340/jrm.v53.688.
[48] Lund A. Measuring usability with the USE Questionnaire. Usability and user experience newsletter of the STC usability SIG; 2001.
[49] O'Cathain A, Hoddinott P, Lewin S, et al. Maximising the impact of qualitative research in feasibility studies for randomised controlled trials: guidance for researchers. Pilot Feasibility Stud. 2015;1(1):32. doi: 10.1186/s40814-015-0026-y.
[50] Eldridge SM, Chan CL, Campbell MJ, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. BMJ. 2016;355:i5239. doi: 10.1136/bmj.i5239.
[51] Sullivan GM, Feinn R. Using effect size—or why the P value is not enough. J Grad Med Educ. 2012;4(3):279–282. doi: 10.4300/JGME-D-12-00156.1.
[52] Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol. 2006;3(2):77–101. doi: 10.1191/1478088706qp063oa.
[53] Finlayson M, Al-Mashita L, Sandhu R. Participant diversity in clinical trials of rehabilitation interventions for people with multiple sclerosis: a scoping review. Mult Scler. 2023;29(9):1149–1157. doi: 10.1177/13524585231189670.
[54] Holper L, Coenen M, Weise A, et al. Characterization of functioning in multiple sclerosis using the ICF. J Neurol. 2010;257(1):103–113. doi: 10.1007/s00415-009-5282-4.
[55] Backus D. Increasing physical activity and participation in people with multiple sclerosis: a review. Arch Phys Med Rehabil. 2016;97(9 Suppl):S210–S7. doi: 10.1016/j.apmr.2015.09.027.
[56] Prouskas SE, Chiaravalloti ND, Kant N, et al. Feasibility of cognitive rehabilitation in patients with advanced multiple sclerosis: a pilot study. Mult Scler J Exp Transl Clin. 2021;7(4):20552173211064473. doi: 10.1177/20552173211064473.
[57] Sieber C, Haag C, Polhemus A, et al. Feasibility and scalability of a fitness tracker study: Results from a longitudinal analysis of persons with multiple sclerosis. Front Digit Health. 2023;5:1006932. doi: 10.3389/fdgth.2023.1006932
[58] Threapleton K, Drummond A, Standen P. Virtual rehabilitation: what are the practical barriers for home-based research? Digit Health. 2016;2:2055207616641302. doi: 10.1177/2055207616641302.
[59] Cuesta-Gómez A, Sánchez-Herrera-Baeza P, Oña-Simbaña ED, et al. Effects of virtual reality associated with serious games for upper limb rehabilitation in patients with multiple sclerosis: randomized controlled trial. J Neuroeng Rehabil. 2020;17(1):90. doi: 10.1186/s12984-020-00718-x.
[60] Ozkul C, Guclu-Gunduz A, Yazici G, et al. Effect of immersive virtual reality on balance, mobility, and fatigue in patients with multiple sclerosis: a single-blinded randomized controlled trial. Eur J Integr Med. 2020;35:101092. doi: 10.1016/j.eujim.2020.101092.
[61] Kalron A, Frid L, Fonkatz I, et al. The design, development, and testing of a virtual reality device for upper limb training in people with multiple sclerosis: single-center feasibility study. JMIR Serious Games. 2022;10(3):e36288. doi: 10.2196/36288.
[62] Merhi O, Faugloire E, Flanagan M, et al. Motion sickness, console video games, and head-mounted displays. Hum Factors. 2007;49(5):920–934. doi: 10.1518/001872007X230262.
[63] Pawełczyk W, Olejarz D, Gaweł Z, et al. Understanding cybersickness and presence in seated VR: a foundation for exploring therapeutic applications of immersive virtual environments. J Clin Med. 2025;14(8):2718. doi: 10.3390/jcm14082718.
[64] Gerling K, Dickinson P, Hicks K, et al. Virtual reality games for people using wheelchairs. Proceedings of the 2020 CHI Conference on Human Factors in Computing Systems. New York, NY, USA: Association for Computing Machinery; 2020. https://dl.acm.org/doi/10.1145/3313831.3376265. doi: 10.1145/3313831.3376265.
[65] Matin A, Maduro M, de Leon Pereira R, et al. Effect of timer, top score and leaderboard on performance and motivation in a human computing game. Proceedings of the 15th International Conference on the Foundations of Digital Games [Internet]. New York, NY, USA: Association for Computing Machinery; 2020. https://dl.acm.org/doi/10.1145/3402942.3403000. doi: 10.1145/3402942.3403000.

[66] Plow M, Finlayson M. A qualitative study exploring the usability of Nintendo Wii Fit among persons with multiple sclerosis. Occup Ther Int. 2014;21(1):21–32. doi: 10.1002/oti.1345.
[67] Bertoni R, Mestanza Mattos FG, Porta M, et al. Effects of immersive virtual reality on upper limb function in subjects with multiple sclerosis: a cross-over study. Mult Scler Relat Disord. 2022;65:104004. doi: 10.1016/j.msard.2022.104004.
[68] Maris A, Coninx K, Seelen H, et al. The impact of robot-mediated adaptive I-TRAVLE training on impaired upper limb function in chronic stroke and multiple sclerosis. Disabil Rehabil Assist Technol. 2018;13(1):1–9. doi: 10.1080/17483107.2016.1278467.
[69] Jonsdottir J, Bertoni R, Lawo M, et al. Serious games for arm rehabilitation of persons with multiple sclerosis. A randomized controlled pilot study. Mult Scler Relat Disord. 2018;19:25–29. doi: 10.1016/j.msard.2017.10.010.
[70] Jonsdottir J, Perini G, Ascolese A, et al. Unilateral arm rehabilitation for persons with multiple sclerosis using serious games in a virtual reality approach: bilateral treatment effect? Mult Scler Relat Disord. 2019;35:76–82. doi: 10.1016/j.msard.2019.07.010.
[71] Lamers I, Cattaneo D, Chen CC, et al. Associations of upper limb disability measures on different levels of the international classification of functioning, disability and health in people with multiple sclerosis. Phys Ther. 2015;95(1):65–75. doi: 10.2522/ptj.20130588.
[72] Singh ND, M. Sample size calculator for comparing two independent means [Internet]. [cited 2025 Dec 21]. Available from: https://statulator.com/SampleSize/ss2M.html.
[73] Ozdogar AT, Ertekin O, Kahraman T, et al. Effect of video-based exergaming on arm and cognitive function in persons with multiple sclerosis: a randomized controlled trial. Mult Scler Relat Disord. 2020;40:101966. doi: 10.1016/j.msard.2020.101966.
[74] Oña ED, Marcos-Antón S, Copaci DS, et al. Effects of EMG-controlled video games on the upper limb functionality in patients with multiple sclerosis: a feasibility study and development description. Comput Intell Neurosci. 2022;2022(1):3735979–3735916. doi: 10.1155/2022/3735979.
[75] Pau M, Cocco E, Arippa F, et al. An immersive virtual kitchen training system for people with multiple sclerosis: a development and validation study. J Clin Med. 2023;12(9):3222. doi: 10.3390/jcm12093222.