TELE-NEUROREHABILITATION

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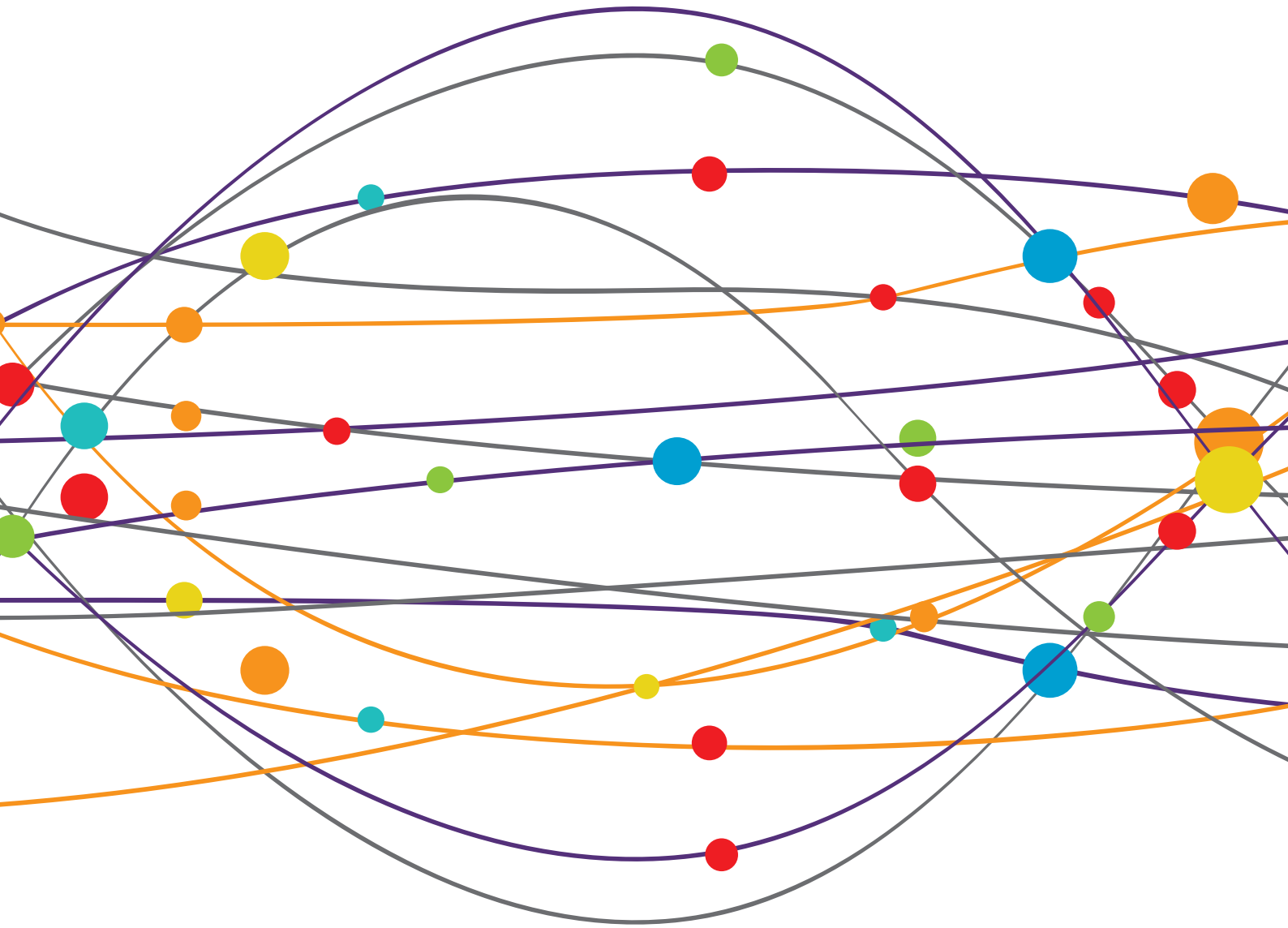

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TELE-NEUROREHABILITATION

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EDITORIAL
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Editorial: Tele-NeuroRehabilitation

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Editorial on the Research Topic

Tele-NeuroRehabilitation

In recent years, the role of telerehabilitation (TR) has gained increased importance across the continuum of the care process. It has been particularly relevant in the last 2 years after the explosion of a pandemic. However, some key points, such as the lack of common and shared methodologies for the delivery of TR treatments and the wide range of possible TR services (including telecounselling, telecare, telemonitoring, and teletherapy) have yet to be further analyzed. Therefore, there is a compelling need for studies to further investigate the effectiveness of many different clinical interventions in TR. The aim of this Research Topic is to present an update on the state of knowledge and expertise in different fields of TR for neurological patients. The papers described in this special issue span a range of neurological deficits, focussing on post-stroke impairments but also covering Parkinson's Disease, MCI, and pediatric neurological impairments. Likewise, while several studies describe preliminary/feasibility results, others report RCTs and comparisons with in-person control groups and conditions. Another theme in this Research Topic is the scoping review of the state of the art in TR in several parts of the world. We highlight those papers briefly here.

As highlighted in a recent Cochrane review, many studies have highlighted that a rehabilitative treatment produces equivalent results whether it is delivered in person or from a distance. While these findings are promising, this important concept cannot simply be generalized and needs to be analyzed in many different settings and patient populations to evaluate the feasibility of new TR approaches. In the article "A Feasibility Study of Expanded Home-Based Telerehabilitation After Stroke," the authors evaluated the feasibility of several expansions, on treatment and assessment, to their prior randomized controlled TR study. The results of this study highlight the feasibility of adding new modules to a home-based system for patients with stroke and open the way to develop future holistic TR approaches, involving many aspects of treating patients at home, from intensive rehabilitation to the management of drugs.

Many articles of this Special Issue are focused on the treatment of aphasia via TR. In the article "Factors associated with adherence to self-managed aphasia therapy practice on a computer. A mixed-methods study alongside a randomized controlled trial," the analysis focuses on factors that may impact on the adherence to self-managed computer-based aphasia treatment. Some factors determining greater or lesser adherence to remote asynchronous treatment emerged; particularly, it has been shown that patients were more willing to use computer therapy if they received supportive stimulation from a speech pathologist.

In the second article on aphasia, "Telerehabilitation for word retrieval deficits in bilinguals with aphasia: effectiveness and reliability as compared to in-person language therapy," the authors verify whether a semantic treatment for word retrieval deficits in bilinguals with post-stroke aphasia

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yielded the same results if administered via TR or in person. Significant improvements were observed and the equivalence of treatment gains and adherence by participants between TR and in-person treatment was confirmed.

The goal of the article "The application of Lexical Retrieval Training in Tablet-Based Speech-Language Intervention" is to verify whether a widely used rehabilitation treatment (Lexical Retrieval Training) can be delivered remotely via a new application activated on a tablet. Initial observations showed that patients were partly able to use the tablet independently and needed to receive help from the operator; furthermore, the participants who received systematic training in the use of the tablet showed greater engagement with the therapy.

The feasibility and effectiveness of a new technological tool, designed for the clinical evaluation and remote treatment of aphasic disorders and cognitive deficits, are evaluated in the article "A virtual randomized control trial of a digital therapeutic for speech, language and cognitive intervention in post-stroke persons with aphasia." The new software, delivered through a tablet, allows the clinician to remotely deliver the exercises in an asynchronous mode, along with a protocol individualized for each patient to improve their adherence to the study. The results highlighted the feasibility and tolerability of remote TR treatment; furthermore, patients in the experimental group showed greater clinical improvements than the control group.

A TR treatment for aphasia delivered 6 years after the onset of aphasia is unusual. Such treatment is described in the article "Integrated Discourse Therapy After Glioblastoma: A Case Report of Face-to-Face and Tele-NeuroRehabilitation (TNR) Treatment Delivery." Although the participant had long-term language disabilities, integrated conversation therapy was administered face-to-face and remotely via TNR. The results showed improvements after both types of treatment administration. Additionally, a satisfaction survey indicated a preference for delivering TNR treatment.

Studies on TR for patients with cognitive disorders are not yet well-defined. The article "Analysis of feasibility, adherence, and appreciation of a newly developed telerehabilitation program for people with Mild Cognitive Impairment (MCI) or Vascular Cognitive Impairment (VCI)" addresses this problem, verifying the feasibility, adherence, and acceptance of a new TR system that provides patients with MCI a multidimensional program to prevent further cognitive decline. The results of this preliminary study showed a good feasibility of the new TR system, and a positive level of adherence to the program and satisfaction with the technological approach.

TR in children requires a very specific approach and careful consideration in terms of delivery. Two papers in this Special Issue address this topic. The article "Adaptive Working Memory Training Can Improve Executive Functioning and Visuo-Spatial Skills in Children with Pre-term Spastic Diplegia (pSD)" shows the results of a study aimed at improving executive function and visuo-spatial skills with evidence-based training focused on working memory (WM) in children with pSD. The treatment was remotely delivered to the patients' homes. The results showed an improvement in targeted WM abilities and generalization to other neuropsychological functions, such as visuo-spatial processing, inhibition, and phonological processing.

The article "Feasibility Analysis of CareToy-Revised Early Intervention in Infants at High Risk for Cerebral Palsy (CP)" evaluates a new technological system (CareToy-CT) that provides via TR a highly personalized, family-centered, home-based early intervention for young infants. CT, already used with pre-teens without brain injury, has been adapted for CP high-risk infants. The preliminary reports evidenced the feasibility of this innovative early intervention in infants at high risk for CP.

The feasibility of a new TR technological system is evaluated in the article "Exergaming as part of telerehabilitation can be adapted to outpatient training: preliminary results of a non-randomized pilot study in Parkinson's disease." The authors built a TR exergaming system, with virtual pick & place tasks for small hand movements, that was designed specifically for PD patients. The preliminary results of a pilot study confirmed that this home exergame, delivered by TR support, can provide clinical efficacy comparable to that of hospital training. In addition, the exergame looks motivating and easy to use.

The innovative aim of assessing whether teleassement is feasible in post-stroke patients is assessed in the article "Remote Assessment of Post-Stroke Elbow Function Using Internet-Based Telerobotics: A Proof-of-Concept Study." The authors created a system with a master robot interacting with a doctor and a slave robot interacting with the elbow of a subject with a stroke, linked together by the Internet. To test the feasibility of remote assessment in an extreme scenario, the teleassessment examiner was in Bethesda (USA) and stroke patients were in Seoul (South Korea). The results of this pilot study showed that this innovative telerobotic evaluation is feasible even in the worst situation.

A relevant trend in TR is the implementation of multidimensional rehabilitation systems, to make the continuity of care more complete. This multidimensional concept emerges in the article "Virtual reality for motor and cognitive rehabilitation from clinic to home: A pilot feasibility and efficacy study for persons with chronic stroke." The feasibility of an innovative digital system to deliver together motor and cognitive rehabilitation treatments is compared in the clinical context and at home. The results showed that the protocol is feasible and the satisfaction and adherence to the treatment were good in both conditions.

From the perspective of TR as a multidimensional system, the social networks in which post-stroke patients live are relevant. The article "Social network structure is related to functional improvement from home-based telerehabilitation after stroke" addresses this aspect. A pilot group of post-stroke patients underwent periodic assessments for motor function and mood and remote supervision through a TR system. The social network of TR patients was positively correlated with the improvement of the clinical picture and appeared wider than that of the control group, highlighting that the strengthening of the social network could be crucial to improving the effects of TR.

A TR approach for people in the vegetative state (VS) or minimally conscious state (MCS) is uncommon. The article "Telemonitoring of patients with chronic traumatic brain injury: a pilot study" evaluates a new specific telemonitoring program,

based on an advanced video-conferencing system and wearable monitoring devices. A comparison between a group of patients monitored at home through the new TR program and a group hospitalized in a traditional long standing hospital showed a trend toward a better clinical picture and a lower daily cost of care in patients treated at home.

The difficulties of patients with chronic neurological disabilities and their caregivers who attend clinical visits in specialized centers are analyzed in the article "The Time Burden of Specialty Clinic Visits in Persons with Neurologic Disease: A Case for Universal Telemedicine Coverage." A specific survey showed that many patients and caregivers experienced severe problems, transportation difficulties, travel times, and daily schedule changes. The results of this survey underscore the potential role of TR in minimizing this burden.

Balance instability is a frequent and severely disabling symptom in Parkinson's patients. On the other hand, many studies have shown that Tai Chi is an aerobic exercise that improves the ability to balance and prevents falls in elderly people. These observations lead to a hypothesis that a mobile phone application combined with a Tai Chi intervention may be effective in improving the balance ability of patients with PD. To verify this hypothesis, the article "A mobile phone App-based Tai Chi training in Parkinson's disease (PD): protocol for a randomized control study" describes the protocol for a proposed single-blind RCT.

Despite its growing body of literature and the scope of services in more developed countries, telerehabilitation continues to face challenges and obstacles to its emergence in less developed countries. Three articles in this special issue focus on the situation of TR in different countries.

In the article "Challenges to the Emergence of Telerehabilitation in a Developing Country: A Systematic Review" the authors focused on the situation in the Philippines. This review was based on an extensive literary search, including gray literature. The overall conclusion is a paucity of data on TR in the Philippines. An alarming detail is that the most common barriers (slow internet speeds, legal concerns, and skepticism) involve all three key factors necessary for the realization of a TR service: technical, organizational, and human.

The article "Telemedicine Guidelines in South East Asia (SEA)—A Scoping Review" aims to explore and compare guidelines on telehealth and telemedicine in South East Asian countries. After a very large search, it emerged that only five countries contained some form of guidelines on telemedicine; the National Telemedicine Guidelines of Singapore are the most comprehensive guidelines in the SEA region and the only one comparable with other telemedicine guidelines worldwide.

The article "Tele-Neuro-Rehabilitation in Italy: state of the art and future perspectives" evaluates the role of telerehabilitation in Italy, as regards motor and cognitive rehabilitation programs. The analysis of this review shows that the studies on TR achieved satisfactory results, however, the quality of the research needs to be significantly improved to clarify the benefits and risks of remote care. Furthermore, the samples from these studies are small, making the results of little relevance to a substantial economic analysis.

In the article "Using the technology acceptance model to identify factors that predict the likelihood of adopting tele-neurorehabilitation," some predictors that could explain why teleneurorehabilitation has not yet reached mainstream adoption, are discussed. The data analysis suggests that poor computer self-efficacy, high computer anxiety, low perception of usefulness, and a belief that the technology is not user-friendly are significant predictors of an individual's likelihood to use TR. The authors underline that if TR moves too soon from the domain of research to become the core business of the health sector, key stakeholders will face barriers that have consistently hindered adoption.

The editors hope that this collection of articles sheds some light on the barriers and facilitators to the advancement of telerehabilitation in neurological patient populations. The innovative research being done in this sphere will no doubt lead to better outcomes for our patients and improved access to the services they need, even in pandemic circumstances.

AUTHOR CONTRIBUTIONS

PT, AH, N-JP, and SK participated in the same way in the editing of the text. All authors contributed to the article and approved the submitted version.

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SYSTEMATIC REVIEW
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Challenges to the Emergence of Telerehabilitation in a Developing Country: A Systematic Review

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Background: Despite being known abroad as a viable alternative to face-to-face consultation and therapy, telerehabilitation has not fully emerged in developing countries like the Philippines. In the midst of the coronavirus disease 2019 (COVID-19) pandemic, wherein social distancing disrupted the in-clinic delivery of rehabilitation services, Filipinos attempted to explore telerehabilitation. However, several hindrances were observed especially during the pre-implementation phase of telerehabilitation, necessitating a review of existing local evidences.

Objective: We aimed to determine the challenges faced by telerehabilitation in the Philippines.

Method: We searched until March 2020 through PubMed, Scopus, Embase, Cochrane Library, and HeRDIN for telerehabilitation-related publications wherein Filipinos were involved as investigator or population. Because of the hypothesized low number of scientific outputs on telerehabilitation locally, we performed handsearching through gray literature and included relevant papers from different rehabilitation-related professional organizations in the Philippines. We analyzed the papers and extracted the human, organizational, and technical challenges to telerehabilitation or telehealth in general.

Results: We analyzed 21 published and 4 unpublished papers, which were mostly reviews (8), feasibility studies (6), or case reports/series (4). Twelve out of 25 studies engaged patients and physicians in remote teleconsultation, teletherapy, telementoring, or telemonitoring. Patients sought telemedicine or telerehabilitation for general medical conditions (in 3 studies), chronic diseases (2), mental health issues (2), orthopedic problems (2), neurologic conditions (1), communication disorders (1), and cardiac conditions (1). Outcomes in aforementioned studies mostly included telehealth acceptance, facilitators, barriers, and satisfaction. Other studies were related to telehealth governance, legalities, and ethical issues. We identified 18 human, 17 organizational, and 18 technical unique challenges related to telerehabilitation in the Philippines. The most common challenges were slow internet speed (in 10 studies), legal concerns (9), and skepticism (9).

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Conclusion: There is paucity of data on telerehabilitation in the Philippines. Local efforts can focus on exploring or addressing the most pressing human, organizational, and technical challenges to the emergence of telerehabilitation in the country.

Keywords: telemedicine, telerehabilitation, barriers, rehabilitation medicine, healthcare delivery, developing country

INTRODUCTION

Located in Southeast Asia, the Republic of the Philippines consists of an archipelago of 7,641 islands with a land area of more than 300,000 km^2 (1). The country is divided into three large groups of islands, namely, Luzon, Visayas, and Mindanao, and into 17 administrative regions (**Figure 1**) (2, 3). The Philippine National Statistics Office estimated that the total population in the country would reach 110 million in 2020 (4). As of writing, the country has a gross national income per capita of 3,830 USD and remains to be a lower-middle-income economy according to The World Bank (5, 6). The geographical landscape, administrative organization, and growing imbalance between population and resources are among the reasons that contribute to the difficult distribution of healthcare services in the Philippines (7).

Of the estimated 1 billion persons with disabilities (PWD) worldwide, 80% come from low- and middle-income countries (8). Based on the 2017 Global Burden of Disease Study, the three leading causes of years lived with disability (YLDs) are low back pain, headache, and depression (9). The World Health Organization states that the total number of YLDs globally is "linked to health conditions for which rehabilitation is beneficial" (10). Rehabilitation is effective in improving or maintaining the functional independence and quality of life of PWD (8, 10). Despite limited reliable data documenting the need for rehabilitation in low- and middle-income countries, unique local experiences can attest to the prevailing unmet needs of the people amidst meager resources (11).

Telemedicine is the delivery of healthcare services through information and communications technology (ICT) to a different, often distant, site (12). As a telemedicine subset, telerehabilitation (telerehab) is an emerging technology that uses electronic means in remotely conducting evaluation, consultation, therapy, and monitoring to provide rehabilitation care for patients in various locations, such as home, community, nearby health facility, and workplace (11–13). Despite its growing body of literature and scope of services in other, mostly developed, countries, telerehabilitation continues to face challenges or barriers to its emergence in less-developed countries like the Philippines, albeit its practical use to address the widening gap between the supply of and demand for rehabilitation services especially during unprecedented times like the coronavirus disease 2019 (COVID-19) pandemic, wherein face-to-face access to rehabilitation services is hampered (14). In this review, we gathered evidences of previous local attempts at telerehabilitation along with other papers that could help us determine the human, organizational, and technical challenges that beset the emergence of telerehabilitation in the country.

METHODS

This review employed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) consensus statements (15).

Criteria for Study Selection

We considered studies based on the following inclusion criteria: (a) study investigator or population included Filipinos residing in the Philippines; and (b) intervention or topic included any telecommunication technology or process related to the remote delivery of medical or rehabilitation services (i.e., consultation, therapy, mentoring, and monitoring). Studies on telemedicine that focused on other specializations, such as dermatology, internal medicine, ophthalmology, pathology, or radiotherapy, were excluded. There was no restriction to the study design and year of publication or completion. Papers written in either English or Filipino were included, and those whose full text could not be accessed were not excluded to increase yield.

Search Methods and Data Analysis

We searched the following electronic healthcare databases until March 2020 for relevant studies: MEDLINE by PubMed, Embase, Scopus, Cochrane Library, and Health Research and Development Information Network (HeRDIN), which is the Philippines' national repository of local studies. Both Medical Subject Headings (MeSH) and free search terms were used as follows: (*"Telemedicine"[Mesh] OR "Telerehabilitation"[Mesh] OR "Remote Consultation"[Mesh] OR "Telenursing"[Mesh] OR telehealth OR telemedicine OR telerehabilitation OR telerehab OR teleneurorehabilitation OR teleconsultation OR teletherapy OR telepractice OR telepsychology OR telenursing) AND ("Philippines"[Mesh] OR Philippine**).

Due to hypothesized limited number of relevant publications from the Philippines, handsearching was done through the gray literature of different local rehabilitation professional organizations, namely, the Philippine Academy of Rehabilitation Medicine (PARM), the Philippine Physical Therapy Association (PPTA), the Philippine Academy of Occupational Therapists, Inc. (PAOT), the Philippine Association of Speech Pathologists (PASP), the Psychological Association of the Philippines (PAP), the Association of Filipino Prosthetists and Orthotists (AFPO), and the Philippine Nurses Association, Inc. (PNA). We contacted members or representatives from aforementioned organizations through text message, phone call, or email to request for relevant information.

We screened the titles and abstracts identified from the search. Relevant articles were obtained in full text (if available) and considered eligible if we could derive the following data

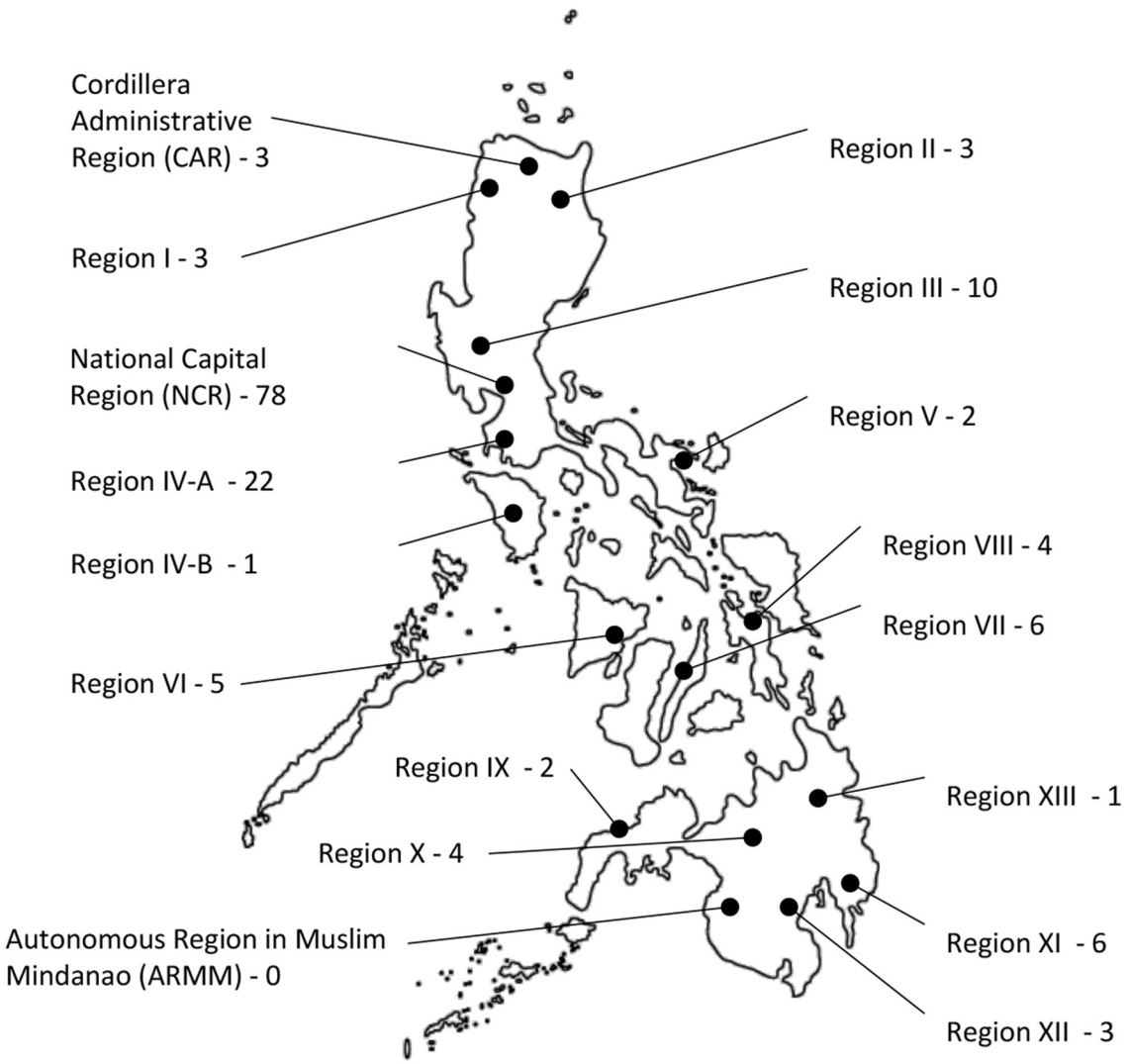

FIGURE 1 | Geographical landscape of the Philippines divided into 17 administrative regions, each with a corresponding number of physiatrists in their place of primary practice.

for analysis: lead author, date of publication or completion, research design, population/target audience/problem identified, telemedicine or telerehabilitation method/concept, outcomes, and challenges to telemedicine or telerehabilitation cited in the results or discussion part. The challenges or barriers were identified, grouped together when applicable, and categorized according to unique human, organizational, and technical factors, based on consensus among study authors.

RESULTS

Characteristics of Included Studies

A total of 130 documents were identified from electronic databases and 6 from handsearching (**Figure 2**). Fifty duplicates were discarded. Out of 86 records screened, 42 were excluded and the rest were assessed for eligibility. Nineteen articles were further excluded because of lack of relevant information. Twenty-five studies were finally analyzed.

Table 1 presents the study design, population, intervention, comparator (if any), outcomes, and challenges related to telerehabilitation of the 25 included studies (21 published and 4 unpublished). The earliest publication was in 2008, while the latest completed study was in early 2020. Studies in *Health Technology and Informatics* and *Acta Medica Philippina* were the most common journals (four studies each). There were eight review papers, six feasibility studies, and four case reports/series among other research designs, which were largely observational. Twelve out of 25 studies engaged patients from remote areas to access healthcare services or information in teleconsultation, teletherapy, telementoring, or telemonitoring. Three studies involved patients with general medical conditions (30, 33, 37), while other studies involved patients with chronic diseases (18,

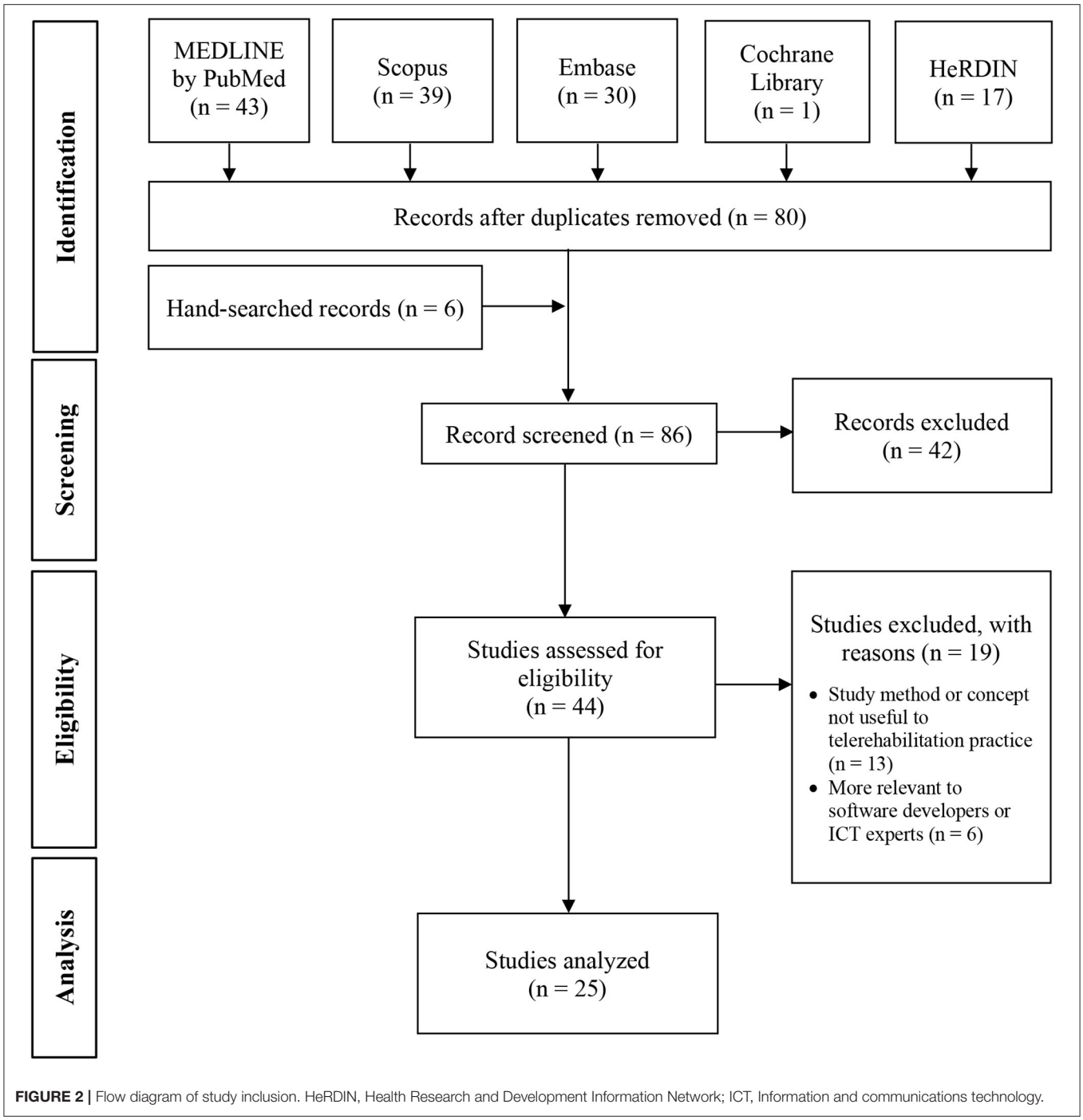

FIGURE 2 | Flow diagram of study inclusion. HeRDIN, Health Research and Development Information Network; ICT, Information and communications technology.

29), mental health issues (17, 26), orthopedic problems (20, 28), neurologic conditions (16), communication disorders (19), and cardiac disease (36).

Teleconsultation meant that a patient consulted with a remote physician (16, 29). Teletherapy meant that a patient received instructions and home exercises demonstrated or supervised by a remote therapist (19, 20). There was one local study that involved physiatrists, physical therapists, occupational therapists, psychologists, and rehabilitation nurses in multi-disciplinary telerehabilitation sessions with a remote community (20). Another study involved speech-language pathologists (19), while two studies involved psychologists (17, 26). Telementoring meant that a remote specialist gave expert advice to a rural physician or healthcare worker co-located with a patient (20, 30, 33, 37). Telemonitoring meant that a gadget or web-based application facilitated asynchronous remote transmission of health-related information or patient reminders (17, 18, 28, 36). The most common electronic methods of

TABLE 1 | Studies relevant to telerehabilitation with Filipinos as study lead author, co-author, or population.

Lead author, year | Study design | Reference	Population/Target audience/Problem	Method	Outcomes	Human (H), organizational (O), and technical (T) challenges to telemedicine/telerehabilitation addressed/discussed in the study
Leochico[a] 2020 | Case report | (16)	2 adults with paraplegia secondary to spinal cord injury were given wheelchairs for free by a charitable institution, but were unable to comply with face-to-face wheelchair follow-up	Consultation and functional retraining through synchronous and asynchronous telerehabilitation using social media application (i.e., Viber™)	Wheelchair assessment using the World Health Organization's wheelchair follow-up form (translated into Filipino) was done through videocall. Wheelchair modifications and exercise recommendations were given. The patients were satisfied with the follow-up via telerehabilitation, obviating the need for immediate face-to-face follow-up	H: Patients' skepticism and misconceptions about telerehabilitation; lack of e-health literacy; resistance to change O: No available secure platform dedicated to telerehab; lack of local telerehab guidelines T: Slow internet
Clough[a] 2019 | Survey | (17)	524 adults from Australia, Iran, Philippines, and South Africa with prior telemedicine experience	Online survey on potential utilization of e-mental health services	Most participants were willing to access e-health programs	H: Lack of knowledge about e-mental health services and how to access them; lack of smartphone, computer, or internet access O: Lack of methods to secure personal information; lack of freedom to use e-mental health services
Hernandez[a] 2019 | Feasibility | (18)	Patients with chronic diseases	"Nurse Chatbot" with artificial intelligence	Chatbot can improve patient access to healthcare information	H: Lack of technology acceptance O: Lack of safeguards against privacy breach, misuse, non-transparency, abuse, human rights violation; lack of clear protocols on data encryption, cybersecurity, and informed consent T: Poor natural language processing and automated response of chatbots; conversational ambiguities; lack of empathy in e-health transactions
Ponciano-Villafania[a] 2018 | Case report | (19)	2 elderly patients with communication disorders referred by rural-based rehabilitation specialist	Patients underwent 4 telerehabilitation sessions with a remotely located speech pathologist	Internet was slower at 7 megabits per second (Mbps) than the ideal speed (10 Mbps). Video and instant messaging using MacBook™ laptop were feasible. Participants expressed benefits from telerehabilitation	H: Lack of technical knowledge among rehabilitation providers O: Lack of telerehabilitation guidelines for full-scale implementation; lack of updated community-based rehabilitation policies and trainings T: Expensive equipment; slow internet
Leochico[a] 2017 | Case report | (20)	Rural-based elderly post-knee arthroplasty could not access face-to-face rehabilitation services	Medical interns in the rural area referred the patient to urban-based telerehabilitation providers through Skype™	Stakeholders (i.e., patient, caregiver, students, community health workers, & telerehabilitation providers) met their needs and expectations	H: Inadequate knowledge and skills in telepresenting and telementoring O: Time-consuming in terms of setup, logistics, consultation, teaching, and technical troubleshooting; lack of professional technical support in the community; lack of exercise equipment T: Fluctuating internet; unclear video projection; unsecure videoconferencing telemedicine application
Mandirola-Brieux[b] 2017 | Survey | (21)	Medical informatics experts	Participants were asked about their e-health perceptions on: - breaking the culture of paper - use of local language - cultural idiosyncrasies	Cultural barriers were found to be among the most important barriers in implementing e-health	H: Most doctors prefer physical records; paper culture O: Difficult e-health implementation T: Electronic records are difficult to use and sustain

(Continued)

TABLE 1 | Continued

Lead author, year | Study design | Reference	Population/Target audience/Problem	Method	Outcomes	Human (H), organizational (O), and technical (T) challenges to telemedicine/telerehabilitation addressed/discussed in the study
Ho[c] 2016 | Review | (22)	Policymakers, stakeholders	"Resilient health system framework" was proposed as guide to scale-up digital health and universal healthcare	The framework was built on three interlocked platforms: - leadership, policy, and governance; - health resource capacity; - information and communications infrastructure (infostructure)	H: Lack of patient engagement due to complex medical advice, poor telecommunication skills, and paternalistic medicine O: Lack of standards to ensure e-health interoperability across organizations and countries; lack of digital health policies and resources T: E-health applications lack contextualization and interoperability across practice settings and devices
Fernandez-Marcelo[c] 2016 | Qualitative research | (23)	Policymakers, researchers, educators, healthcare providers, telehealth enthusiasts	Public fora with Department of Health, local government units, non-government organizations, academe, medical professional organizations, private sectors	Recommendations on the National Telehealth Service Program Administrative Order were given in terms of: - governance; - capacity-building; - financing; - regulation; - ethics; - data privacy	O: Lack of engagement among patient groups, clinical experts, private sectors, and local governments; lack of measures to ensure privacy and information security; unclear stakeholders' accountability; lack of providers' training, accreditation, and regulation; unclear government-subsidized financing options; lack of national policy framework; poor national ICT infrastructure
Mendoza[a] 2016 | Review | Mendoza et al., unpublished	Problem: There is limited information about the use of telerehabilitation in developing countries	Publications on telerehabilitation across different allied health disciplines from developing countries were searched.	Publications came from Brazil, China, South Korea, South Africa, Taiwan, Hong Kong, Iran, Israel, Nigeria, Colombia, Chile, Guatemala, Nicaragua, Thailand, and Pakistan. Most studies were from higher-middle-income countries and focused on telerehabilitation interventions and assessments	H: Limited knowledge and mixed attitudes and satisfaction toward telerehab among physical therapists, occupational therapists, and speech-language pathologists; lack of acceptance; lack of personal communication/rapport; lack of digital literacy O: Lack of studies from developing countries; lack of validated data collection tools; lack of government support, continuing training, and resources; lack of guidelines to determine appropriate populations suitable for telerehab; environmental constraints T: Inability to provide manual therapy/assistance through this technology; lack of interoperability across different software applications; limited internet coverage; equipment failure
Patdu[c] 2016 | Qualitative research | (24)	Policymakers, researchers, educators, healthcare providers, telehealth enthusiasts	Roundtable discussions with Department of Health, information technologists, lawyers	Having no law regulating telehealth in the Philippines, the following were discussed: - practice of telemedicine; - liability issues; - data privacy	O: Lack of laws governing telemedicine practice in the country; lack of security measures for sensitive information
Umali[c] 2016 | Mixed methods | (25)	Policymakers, researchers, healthcare providers, telehealth enthusiasts	Review of policies and guidelines pertinent to e-health ethics in the Philippines; focus group discussion and key informant interviews	Gaps and lapses related to ethics were prevalent. There was a need to emphasize ethics in the development and implementation of e-health policies	O: Lack of guidelines to ensure ethical telehealth practice in the Philippines; unclear roles and liabilities

(Continued)

TABLE 1 | Continued

Lead author, year | Study design | Reference	Population/Target audience/Problem	Method	Outcomes	Human (H), organizational (O), and technical (T) challenges to telemedicine/telerehabilitation addressed/discussed in the study
Ramos[c] 2019 | Validation | (26)	College students	*Psychologist in a Pocket* (PiaP): mental m-health application	Significant positive correlations were found between PiaP and psychological tests. PiaP's approach to depression screening was comparable with gold standard (Beck's Depression Inventory)	H: High dropout rate in remote e-health trials; poor adherence to mental healthcare applications T: Lack of perfect correlation between the software application and face-to-face psychological tests; inability of the app to detect behavioral signs of depression, which could not be expressed through text
Laron[b] 2015 | Review | Laron et al., unpublished	Physical therapists, occupational therapists, speech-language pathologists	Literature review on telerehabilitation knowledge, attitudes, and perceptions among therapists	Most studies utilized customized, non-validated questionnaires. Attitudes and perceptions were mostly positive. One study showed low knowledge	H: Incomplete acceptance; apprehensions related to virtual environment, rapport, accuracy, effectiveness, efficiency, suitability to healthcare needs and resources, safety O: Lack of government support, continuing training, and resources T: Inability of the technology to provide manual assistance during therapy; lack of flexibility across available telerehab software applications; limited internet coverage
Marcelo[c] 2015 | Review | (27)	Policymakers, stakeholders	Government-recognized or public-funded national telehealth programs in Asia were searched along with their corresponding state of governance and management	Asian countries with funded telehealth programs were Bangladesh, India, Indonesia, Malaysia, Maldives, Philippines, and Sri Lanka	O: Challenges with governance, management, and sustainability of operations; lack of ICT governance framework
Mojica[a] 2014 | Pilot | (28)	40 lower limb amputees in an urban community	The *Amputee Screening through Cellphone Networking* (ASCENT) application was designed to detect amputees in the community	ASCENT showed excellent overall agreement and inter-observer reliability among medical interns and health workers in the community. It was an easy and fast way to screen and refer amputees through internet-enabled asynchronous telerehabilitation	H: Need to train end-users O: Need to partner with a software developer T: Web-based app was Java-enabled, which could be slow and memory-consuming; non-editable referral once sent; relied on network signal
Sahu[a] 2014 | Review | (29)	Patients with chronic diseases in Asia and Africa	Delivery of health information through cellphone	Mobile text messaging between patient and healthcare provider was convenient and effective in health monitoring, self-management of chronic diseases, delivery of individualized pharmaceutical care, medication adherence, and public health awareness	H: Need to adjust mindset of end-users, empower patients with medical knowledge in everyday language, and ensure them of confidentiality O: Limited evidence, especially on cost–benefit ratio, long-term benefits, and different study settings; lack of guidelines to ensure quality electronic delivery of healthcare; lack of standardized approach for the design, development, and evaluation of m-health technologies T: Undependable broadband internet speed; m-health technologies lack good display and adequate security controls; lack of intelligent algorithms to identify clinically significant events before notifying caregivers

(Continued)

TABLE 1 | Continued

Lead author, year | Study design | Reference	Population/Target audience/Problem	Method	Outcomes	Human (H), organizational (O), and technical (T) challenges to telemedicine/telerehabilitation addressed/discussed in the study
Macrohon[a] 2013 | Cohort | (30)	8 rural municipal health officers and 39 patients	Teleconsultation with a remote specialist using combined web- (Moodle™) and short messaging system (SMS)-based techniques	Referral via SMS was more common. High satisfaction was noted	H: Apprehensions on convenience, costs, sustainability, and privacy; unavailability and apprehensions of urban-based specialists in the specific field of expertise O: Low utilization of teleconsultation program; time-consuming process; little time to tele-refer amidst other clinical/administrative responsibilities; lack of community-based technical support; vague legalities and reimbursements of teleconsultations T: Variable internet bandwidth, network signal, and electricity across different rural areas; effort-requiring computer-based programs
Caranguian[c] 2012 | Feasibility | (31)	Problem: The ISO/IEEE 11073 Personal Health Device Standards have not adequately addressed security and authentication of medical devices.	To address security, two approaches were tested: direct software implementation and use of embedded security modules (ESM)	ESM offered greater security advantage, such as secure keys storage	T: Lack of telemedicine system integrity
Fernandez-Marcelo[c] 2012 | Mixed methods | (32)	Policymakers, researchers, educators, healthcare providers, telehealth enthusiasts	Review, key informant interviews, and conferences were done to explore e-health capacities in research, education, and service	Awareness of e-health was promoted by stakeholders	O: Lack of policies and standards, capability-building, and multi-sectoral collaborations
Macrohon[a] 2011 | Feasibility | (33)	Rural patients	Teleconsultation program, consisting of cellphone- and web-based methods, used by rural physicians to refer cases to urban specialists	Majority used cellphone-based methods (texting more than calling)	H: Concerns about costs and waiting time to receive responses to referrals T: Need to boot-up equipment when using computers; variable broadband internet speed
Marcelo[c] 2011 | Mixed methods | (34)	Problems existed in building internal capacity for telehealth in developing countries	Literature review and key informant interviews were done to explore partnerships, standards, and interoperability as components of health informatics programs	Developing countries needed to enhance capacities for m-health technologies	O: Difficult networking across archipelago; limited investments in building capacity for health informatics; government's slow adoption of health informatics standards and lack of collaboration with developed institutions due to social, political, and economic challenges; lack of human resources and training to support health informatics; lack of privacy frameworks and standards for interoperability T: Impractical conventional hardware (servers, workstations) in underserved areas with power fluctuations; inadequate technology infrastructure; licensed proprietary software limiting ability of local programmers to observe and improve software engineering practices
Marcelo[c] 2010 | Review | (35)	Problem: Many health information systems (HIS) in developing countries fail during implementation	Existing international HIS were reviewed	Successful HIS and frameworks could serve as models for resource-constrained healthcare settings	O: Lack of or unsustainable HIS; non-adoption of existing successful frameworks

(Continued)

TABLE 1 | Continued

Lead author, year | Study design | Reference	Population/Target audience/Problem	Method	Outcomes	Human (H), organizational (O), and technical (T) challenges to telemedicine/telerehabilitation addressed/discussed in the study
Alis[a] 2009 | Feasibility | (36)	30 patients with pre-diagnosed cardiac pathologies	Real-time information on cardiac status of patients from a telemonitoring device was sent to off-site specialists via mobile phone	Patients were classified as follows: - normal (86.7% accuracy); - congestive heart failure (86.7%); - atrial fibrillation (80.0%)	T: Unreliable wired infrastructure; limited internet bandwidth for media transfer
Gavino[a] 2008 | Case series | (37)	34 doctors-to-the-barrios	Doctors in rural areas referred patients to urban specialists through text	Extensive wireless network coverage (>90% of the country) in rural areas made mobile phones more accessible than web-based solutions	T: Inaccessible internet-based methods; limited (160) characters in a single text message using non-smartphones
Nguyen[c] 2008 | Review | (38)	Policymakers, healthcare providers, telehealth enthusiasts	Review of healthcare informatics in Singapore, Cambodia, Malaysia, Thailand, Laos, Philippines, and Vietnam	Healthcare management varied widely in Southeast Asia from being well-developed in Singapore to being underdeveloped in Laos, affected by various political, economic, societal, cultural, and educational factors	O: Poor healthcare financing; lack of harmonization between private and public sectors; unsustainable e-health programs; lack of ICT support

[a]Engaged patients and physicians in teleconsultation, teletherapy, telementoring, or telemonitoring. [b]Focused on awareness and other factors affecting telemedicine or telerehabilitation. [c]Related to telehealth-related governance, national policies, legalities, and ethics. ICT, Information and communications technology; ISO/IEEE, International Organization for Standardization/Institute of Electrical and Electronics Engineers.

conducting telerehabilitation (i.e., teleconsultation, teletherapy, telementoring, or telemonitoring) used in the local studies were mobile text messaging or short messaging system (SMS) (29, 30, 33, 37), followed by videocall and instant messaging through available social media platforms, such as Viber™ (16), Skype™ (20), or FaceTime™ (19). Two studies conducted teleconsultations through combined web- (i.e., Moodle™) and SMS-based services (30, 33). In general, positive experiences were noted from patients and rural physicians. The concerns raised, however, were mostly related to internet speed and data privacy issues.

The rest of the studies were related to telerehabilitation acceptance (Laron et al., unpublished; Mendoza et al., unpublished), telehealth-related governance (22, 32, 34, 35, 38), national programs or policies (23, 24, 27), legal issues (24), data privacy and security concerns (24, 31, 39) and ethical dilemmas (24, 25). Majority of the authors of these papers were affiliated with the National Telehealth Center of the National Institutes of Health at the University of the Philippines Manila. It was found that no Philippine law specific to telehealth has been approved yet according to Patdu and Tenorio (24). Nonetheless, there were initial efforts to lobby for telehealth by addressing funding, legal, ethical, and administrative challenges (23, 24, 32, 40).

Challenges to Telerehabilitation

While **Table 1** contains the human, organizational, and technical challenges cited in each study, **Table 2** groups together similar challenges and organizes them into these three categories in order of frequency. In terms of human factors, the most commonly discussed challenges in the included studies were lack of acceptance of telehealth among stakeholders (in 9 studies), lack of knowledge and skills needed in e-health (6), and apprehensions related to data privacy (4). Among the organizational factors, which account for the highest percentage (42%) of the total frequency of citations of identified barriers, the most pressing were the lack of national e-health policies or laws (in 9 studies), health information systems framework (8), governance (5), and data privacy measures (5). Among all individual factors across categories, the internet was the overall number 1 challenge to telehealth in the Philippines, as mentioned in at least 10 studies.

Since human factors pertain to internal challenges (or within the person) (41), majority of those listed in **Table 2A** are interrelated with one another and may contribute to skepticism. Several studies have evaluated or attempted to address the lack of awareness and acceptance of telemedicine among stakeholders. Research fora, stakeholders' meetings, campaigns, and conferences conducted by Fernandez-Marcelo et al. in 2012 stimulated awareness of telehealth in a wider scale locally (32). The National Telehealth Service Program of the Department of Health was an important milestone in spreading telehealth awareness in rural areas, as shown by Macrohon and Cristobal (30, 33) and Gavino et al. (37). Local studies by Leochico and Mojica (20), Leochico and Valera (16), and Mojica et al. (28) in the Philippine General Hospital sprung awareness of telerehabilitation in particular. Two unpublished reviews found positive attitudes and limited experience with telerehabilitation among allied rehabilitation professionals in developing countries

TABLE 2 | Frequency of human, organizational, and technical challenges to telerehabilitation in the Philippines cited in included studies.

Challenges	References	Frequency
A. HUMAN FACTORS		**41**
1. Skepticism/lack of acceptance/resistance to change/negative attitudes	[(16–18, 21, 22, 29, 30); Laron et al., unpublished; Mendoza et al., unpublished]	9
2. Lack of technical or digital knowledge and skills; need for training	[(16, 17, 19, 20, 28); Mendoza et al., unpublished]	6
3. Concerned about data privacy/confidentiality/security	(17, 18, 29, 30)	4
4. Lack of awareness of telemedicine/telerehabilitation	(16, 17, 29)	3
5. Concerned about costs	(30, 33)	2
6. Concerned about national laws/legalities	(17, 18)	2
7. Inadequate rapport	(Laron et al., unpublished; Mendoza et al., unpublished)	2
8. Lack of patient participation/poor adherence	(22, 26)	2
9. Perceived inconvenience/time-consuming	(30, 33)	2
10. Concerned about appropriateness	Laron et al., unpublished	1
11. Concerned about effectiveness	Laron et al., unpublished	1
12. Concerned about efficiency	Laron et al., unpublished	1
13. Concerned about informed consent	(18)	1
14. Concerned about safety	Laron et al., unpublished	1
15. Concerned about sustainability	(30)	1
16. Lack of satisfaction	Mendoza et al., unpublished	1
17. Paper culture	(21)	1
18. Poor telecommunication skills	(22)	1
B. ORGANIZATIONAL FACTORS		**60**
1. Lack of national e-health policies/laws/regulations	(22–25, 27, 29, 30, 32, 34)	9
2. Need for ICT infrastructure/HIS framework/partnerships	(23, 27–29, 32, 34, 35, 38)	8
3. Lack of governance/support	[(27, 32, 34); Laron et al., unpublished; Mendoza et al., unpublished]	5
4. Lack of platforms/measures that ensure privacy and security	(16, 23, 24, 30, 34)	5
5. Financing and reimbursement problems	(23, 30, 34, 38)	4
6. Lack of e-health resources	[(22, 30); Laron et al., unpublished; Mendoza et al., unpublished]	4
7. Lack of technical support	(20, 30, 34, 38)	4
8. Lack of telerehabilitation guidelines/standards	[(16, 19, 22); Mendoza et al., unpublished]	4
9. Lack of training for providers	[(23, 34); Laron et al., unpublished; Mendoza et al., unpublished]	4
10. Unclear accountability/roles/liabilities	(23, 25, 30)	3
11. Difficult implementation; unsustainable program; low utilization	(21, 30)	2
12. Lack of studies/evidence	[(29); Mendoza et al., unpublished]	2
13. Time-consuming process; busy work schedule	(20, 30)	2
14. Environmental constraints to telehealth	Mendoza et al., unpublished	1
15. Lack of exercise equipment	(20)	1
16. Lack of updated community-based rehabilitation policies	(19)	1
17. Lack of validated data collection tools/performance measures	Mendoza et al., unpublished	1
C. TECHNICAL FACTORS		**42**
1. Slow internet/limited internet coverage	[(16, 19, 20, 29, 30, 33, 34, 36); Laron et al., unpublished; Mendoza et al., unpublished]	10
2. Difficult or time-consuming to use/sustain	(21, 30, 33)	3
3. Lack of security	(20, 29, 31)	3
4. Lacks interoperability	[(22); Laron et al., unpublished; Mendoza et al., unpublished]	3
5. Software limitations/inadequacies	(26, 28, 37)	3
6. Dependence on electricity	(30, 34)	2
7. Dependence on internet	(28, 37)	2
8. Difficult examination/treatment	(Laron et al., unpublished; Mendoza et al., unpublished)	2
9. Hardware failure/defects/limitations	[(34); Mendoza et al., unpublished]	2
10. Inadequate infrastructure	(34, 36)	2
11. Limitations of artificial intelligence	(18, 29)	2
12. Unclear video/display	(20, 29)	2
13. Expensive	(19)	1
14. Lacks capacity for empathy	(18)	1
15. Lacks contextualization	(22)	1
16. Lacks correlation with face-to-face assessment/treatment	(26)	1
17. Licensed proprietary software	(34)	1
18. Limited network coverage	(30)	1

ICT, information and communications technology; HIS, health information systems.

(Laron et al., unpublished). However, no published study related to telerehabilitation knowledge, attitudes, and perceptions among healthcare professionals was found from the Philippines. The study by Mandirola-Brieux et al. stated that cultural factors played a role in the acceptance of e-health programs (21). A systematic review on the role of telehealth in African and Asian countries showed that mobile text messaging was the most commonly accepted telehealth method among patients with chronic diseases (29).

There were several factors that were classified into more than one category, depending on the context in which the factor was discussed in individual studies. For instance, challenges related

to national laws and guidelines, albeit more commonly discussed as an organizational factor, were contributory to human factors (i.e., apprehensions and various concerns). Meanwhile, issues on data privacy or security were listed under each category. Another recurring theme across all categories was related to technical aspect of e-health, cited as lack of digital knowledge and skills (under human factors), lack of technical support and training (under organizational factors), and technologies that were difficult to use, along with software and hardware issues (under technical factors).

DISCUSSION

Our study found 53 unique, albeit interrelated, challenges in the literature that could affect the emergence of telerehabilitation in the Philippines. This review was driven by the difficulties experienced first-hand by the authors during the pre-implementation and implementation periods of telerehabilitation in local private and public healthcare settings in response to COVID-19. Probably similar to most developing countries without pre-existing telerehabilitation guidelines, rehabilitation providers in the Philippines were generally unprepared and apprehensive to adopt telerehabilitation in their practice. Evidences in this review helped us name the felt barriers to telerehabilitation and telehealth in general and categorized them into human, organizational, and technical factors in order of frequency. Overall, organizational factors accounted for the highest number of citations similar to a previous systematic review (42), while the most commonly cited specific factor across all categories was internet connection, as experienced in low- or middle-income countries (43).

Telerehabilitation literature in the Philippines is limited to feasibility studies and case reports. Despite scarce local evidence and experience, telerehab was deemed feasible even before the pandemic to perform remote teleconsultation, teletherapy, telementoring, or telemonitoring mostly for indigent patients in rural areas. As of writing, however, no local telerehabilitation document exists to operationally define various interchangeable terms, such as telehealth, telemedicine, telerehabilitation, teletherapy, telepractice, and telecare among many others used in the different rehabilitation disciplines. More so, there is no guideline on telerehabilitation principles, scope of services, procedure, and regulations that can be applicable across various rehabilitation professional organizations in the country.

Several success stories of national telerehabilitation programs abroad can inspire the eventual emergence of telerehabilitation in the Philippines. For instance, Canada and Australia use telerehabilitation to enhance access across vast geographical landscapes and minimize economic barriers by reducing travel time and costs (44, 45). Meanwhile, India, a lower-middle-income country (6), has a teleneurorehabilitation program to remotely provide cost-effective services amidst limited medical resources (46). Each country that has adopted telerehabilitation even before the pandemic acts according to the needs of its people and healthcare system.

The rehabilitation needs of the growing population from all over the Philippine archipelago cannot always be addressed face to face because of the barriers of distance, time, costs, manpower, and resources. Center-based rehabilitation services are limited, with more than 50% of the facilities located in urban areas of the National Capital Region (NCR) (47). There are only 216 fellows of good standing recognized by the Philippine Academy of Rehabilitation Medicine, 78 of whom have their primary practice in NCR (**Figure 1**) (47). Among physical therapists (PTs), there are 5,327 members of the Philippine Physical Therapy Association out of the 14,610 licensed PTs (48). Meanwhile, there are 2,985 occupational therapists, 673 speech-language pathologists, and 53 prosthetists–orthotists in the country (49, 50). Included in these numbers are those who might have migrated abroad, changed career, or retired. The greatest proportion of rehabilitation workforce remaining in the Philippines is based in Luzon (51).

Various local rehabilitation services, such as community-based programs, have been in place to support PWD throughout the country. However, efforts to empower rural communities and PWD have been hampered by several challenges, such as low accessibility, high costs, low utilization, and low sustainability (52). Amidst social distancing due to COVID-19, face-to-face rehabilitation might not adequately and safely cope with the continuing demand of PWD. A potentially viable solution is telerehabilitation, but it is also not without challenges.

In line with the Philippine e-Health Systems and Services Act, feasibility and cost-effectiveness studies should be done prior to implementation of telehealth-related programs in healthcare facilities (53). In addition, awareness campaigns, workforce training, capacity-building, and policy-updating are also important measures to ensure sustainable programs (23, 32). In relation to local telerehabilitation experience, however, these crucial steps were bypassed during the COVID-19 pandemic to urgently come up with interim guidelines.

When planning a telerehabilitation program, it should be emphasized that guidelines vary from one healthcare setting to another, depending on human, organizational, and technical factors. First, human (internal) factors include telerehabilitation awareness, acceptance, readiness, knowledge, and skills [Laron et al., unpublished; (41)]. Local studies on these interrelated human factors among different stakeholders (i.e., patient, family or caregiver, healthcare provider, policymakers, third-party payers) are recommended. Second, to address organizational (external) factors, the following are recommended: lobbying for administrative support and funding, formulation of best practice guidelines, work reorganization, agreement on payment schemes and reimbursements, and measures to protect data privacy and safety of stakeholders (23, 27, 53). Lastly, technical factors should be addressed by improving the quantity and quality of tangible (i.e., telerehabilitation equipment and technical support) and intangible e-health resources (i.e., technical skills, information and communications framework or "infostructure") (22). Understanding and addressing such factors are key to successful telerehabilitation initiatives.

As evident during the pandemic, videoconferencing has become relatively more feasible locally compared to earlier

years. During the first quarter of 2017, Akamai, a recognized cloud data network monitoring internet traffic, reported that the Philippines had the largest quarterly increase in internet speed at 26% in the Asia-Pacific region (54). Still, however, the country had the lowest average connection speed at 5.5 megabits per second (Mbps), compared to the global speed of 7.2 Mbps (54). In addition to its slow speed, the internet in the Philippines has not always been cheap with mobile cellular and fixed broadband services amounting to 22.24 and 51.59 USD per month, respectively (55). Although the country has been working on national reforms toward universal internet access (56), we have yet to see improvements in the technology to facilitate e-health access.

As strengths of this study, we were able to contribute to the limited knowledge of telerehabilitation facilitators and barriers in a developing country. We structured our paper following the PRISMA guidelines. We attempted to increase the number of included studies by handsearching of gray literature. We analyzed 25 studies and extracted the human, organizational, and technical challenges that might be applicable not only in the Philippines but also in other resource-limited countries. In terms of limitations, a more thorough handsearching of gray literature from other institutions across the archipelago and inclusion of studies from other developing countries could have been done. A more objective screening process could have also increased the number of analyzed studies. Although we attempted to control for this limitation by having more than one reviewer screening each study, potential bias toward rehabilitation medicine has excluded studies from other specialties, whose experiences could have also been rich data sources on telehealth challenges. Another factor that might have influenced our results was individual judgment in analyzing the studies and extracting the barriers and categorizing them into human, organizational, and technical factors. Nonetheless, we tried to address this limitation by consensus meetings. Lastly, the challenges cited in this paper were solely based on secondary data; hence, future large-scale descriptive and analytical studies gathering primary data are recommended.

As more stakeholders recognize the value of telerehabilitation, catalyzed by the COVID-19 pandemic, more efforts can be made to address the various challenges besetting the emergence of telerehabilitation in the country. Researches on telerehabilitation and policy changes through Delphi method can help us respond better to the World Health Organization's *Rehabilitation 2030 Call to Action* to improve access to rehabilitation services (10, 42, 57). A lot of work has yet to be done to address the human, organizational, and technical challenges to telerehabilitation, but we can be guided by existing local and international evidences, along with experts in telehealth and medical informatics, to avoid costly and time-consuming trial-and-error attempts.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

CL conceived the idea and wrote the initial drafts and final revisions of the manuscript. AE, SI, and JM made substantial contributions in the content and format of the revised versions. All authors contributed to the article and approved the submitted version.

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Tele-Neuro-Rehabilitation in Italy: State of the Art and Future Perspectives

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Current research suggests that the management of neurological diseases, both in adults and children, requires an ever increasing commitment of resources for the national healthcare system (NHS). In Italy, due to the aging of the population, increase in chronicity and morbidity of pathologies, and presence of islands and rural areas, health needs to be supported by innovative technologies. Telemedicine is a method of providing healthcare services at distance, remotely connecting health professionals and patients (or two professionals). In Italy, telemedicine is under development, and the NHS has not yet exploited and independently developed all the possibilities that telemedicine offers. Tele-rehabilitation consists in the use of information and communication technologies for the remote support of rehabilitation services. By allowing "home care," it represents a valid support during the home rehabilitation process. This review is aimed at evaluating the role of telerehabilitation in Italy, with regard to the motor and cognitive rehabilitation programs applied to neurological pathologies, in both pediatric and adult patients. We screened the studies published between 2010 and 2019 on PubMed, Scopus, Cochrane, and Web of Sciences databases. Using the PICO model, the search combined the terms "telerehabilitation"; "neurological disorders"; "neurodegenerative disease," "motor telerehabilitation"; "cognitive rehabilitation." This review showed that telerehabilitation is a promising healthcare tool, as it guarantees continuity of care over time (after discharge) and in space (from hospital to patient's home), especially in patients with stroke. Furthermore, it allows to increase the frequency and intensity of rehabilitation programs, provide individualized rehabilitation treatment in comfortable and familiar environment for patient, monitor and evaluate patients' needs and progress, stimulate patient motivation and achieve better patient satisfaction, verify the results achieved by the patients, and potentially reduce the service costs. Unfortunately, almost all neurorehabilitation studies are characterized by small samples and wide variability of results, and would benefit from standardized procedures, aims and targets. Future telerehabilitation trials should include cost-effectiveness analysis associated with clinical outcomes to better assess the validity of this promising tool.

Keywords: motor rehabilitation, cognitive training, remote rehabilitation, neurological disorders, neurodegenerative diseases

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INTRODUCTION

The National Health System (NHS) undergoes continuous changes, such as reorganization of primary care, integration between different levels of care and continuity of care. Neurological and neurodegenerative disease management, both for adults and children, has a strong impact on the NHS due to the presence of disabilities, with serious economic and social consequences also for families (1, 2). Telemedicine is a method of providing health care services, through the use of Information and Communication Technologies (ICT), in which the health professional and the patient (or two professionals) are far (3). In addition, telemedicine helps overcome patient's mobility problems and reduce NHS costs (4). There are various application areas of telemedicine, including telecardiology, teledermatology, telestroke, and telerehabilitation.

The American Telemedicine Association establishes telerehabilitation as the delivery of rehabilitation services through ICT (5). Telerehabilitation represents an emerging and innovative approach during the home rehabilitation path that the patient undertakes for the improvement of his/her own motor, cognitive or psychological disorders. In particular, tele-neurorehabilitation may provide many types of interventions, including physiotherapy, speech, cognitive and behavioral therapy, occupational therapy, telemonitoring, and teleconsultation (6). Telerehabilitation offers a fair opportunity of access to rehabilitation services for people who live in remote areas or cannot reach the care centers due to physical impairments (7). Indeed, it can guarantee the continuity of care over time (after discharge) and in space (from hospital to patient's home) (8), substantial cost savings (due to the reduction of specialized human resources), an improvement in comfort and patient lifestyle (9), and an increased frequency and adherence to therapy (10). Some authors have observed that patients report high levels of satisfaction with the use of telerehabilitation (7–11), with a decrease in long-term disability, increase in secondary prevention, as well as a better management of the post-acute/chronic phase of disorders (12, 13). Recent studies have shown that the effects of telerehabilitation are comparable to standard care (14–16). A neuroimaging study has demonstrated that telerehabilitation treatments activate the same cortical regions as conventional treatment do (17). However, other studies have highlighted the need to standardize the procedures, aims and targets that characterize this therapeutic modality (18, 19).

Literature data shows that telerehabilitation can be a promising intervention for elderly (20), adults (21), children with neurological diseases (22), as well as for the treatment of motor (23, 24), cognitive (25) and language disorders (26–30). In Italy, the healthcare system could be supported by telemedicine interventions, due to the aging population, the increase in chronicity and morbidity of diseases, and the presence of rural areas, islands, and mountains. However, in Italy, the development of telemedicine is recent, in fact it has been adopted by few hospitals, as disparities exist among the different regions as regards to healthcare provision (2).

Considering the potential of telerehabilitation in the Italian NHS, the aim of this work was to investigate the current use of this innovative tool in Italy, as well as the efficacy of telerehabilitation on motor and cognitive outcomes of neurological disorders, paving the way for the future perspectives of this promising field.

METHODS: SEARCH STRATEGY

This review sought to investigate the potential of telerehabilitation in the Italian NHS. Studies were identified by searching on PubMed, Web Of Science and Cochrane databases. We defined our combination of search terms using a PICO (population, intervention, comparison, outcome) model. Population was limited to neurological and neurodegenerative patients, including neurodevelopmental disorders; intervention included all telerehabilitation project/protocols realized in the Italian NHS; comparison was evaluated considering the standard cognitive and motor rehabilitation techniques; and outcome included any motor and cognitive improvements shown by the patients, efficacy of treatment or feasibility in terms of cost-benefit or usability of telemedicine system.

The search combined the following terms: "telerehabilitation" OR "remote rehabilitation" AND "neurological disorders" OR "neurodegenerative disorders" AND "motor telerehabilitation" OR "cognitive rehabilitation" AND "Italy" OR "Italian NHS." All the results of each database between January 2010 and March 2020 were evaluated for possible inclusion (**Figure 1**). After the removal of the duplicates, all of the articles were evaluated based on the titles and abstracts.

The inclusion criteria were (i) patients with neurological/neurodegenerative disease; (ii) telerehabilitation studied carried out in Italy; (iii) English language; and (v) published in a peer-reviewed journal.

Data extraction was performed on 120 articles, 50 articles were excluded due to duplicates (**Figure 1**). The data were extracted on the basis of the following data: authors, year, and type of publication (for example, conference proceedings, clinical case), characteristics of the participants involved in the study and purpose of the study.

After an accurate revision of full manuscripts, 38 articles satisfied the inclusion/exclusion criteria and the PICO approach (**Table 1**).

TELE-MOTOR REHABILITATION

Telerehabilitation involves the remote delivery of several rehabilitation services through telecommunication technology, including physiotherapy and occupational therapy, thus, providing assistance to patients forced at home without the physical presence of therapists. Some randomized controlled trials (RCT) on motor function rehabilitation have shown that telerehabilitation can have similar effects to conventional therapy (14, 15). Furthermore, functional magnetic resonance imaging has shown that telerehabilitation activates the same cortical regions as conventional treatment does. Previous

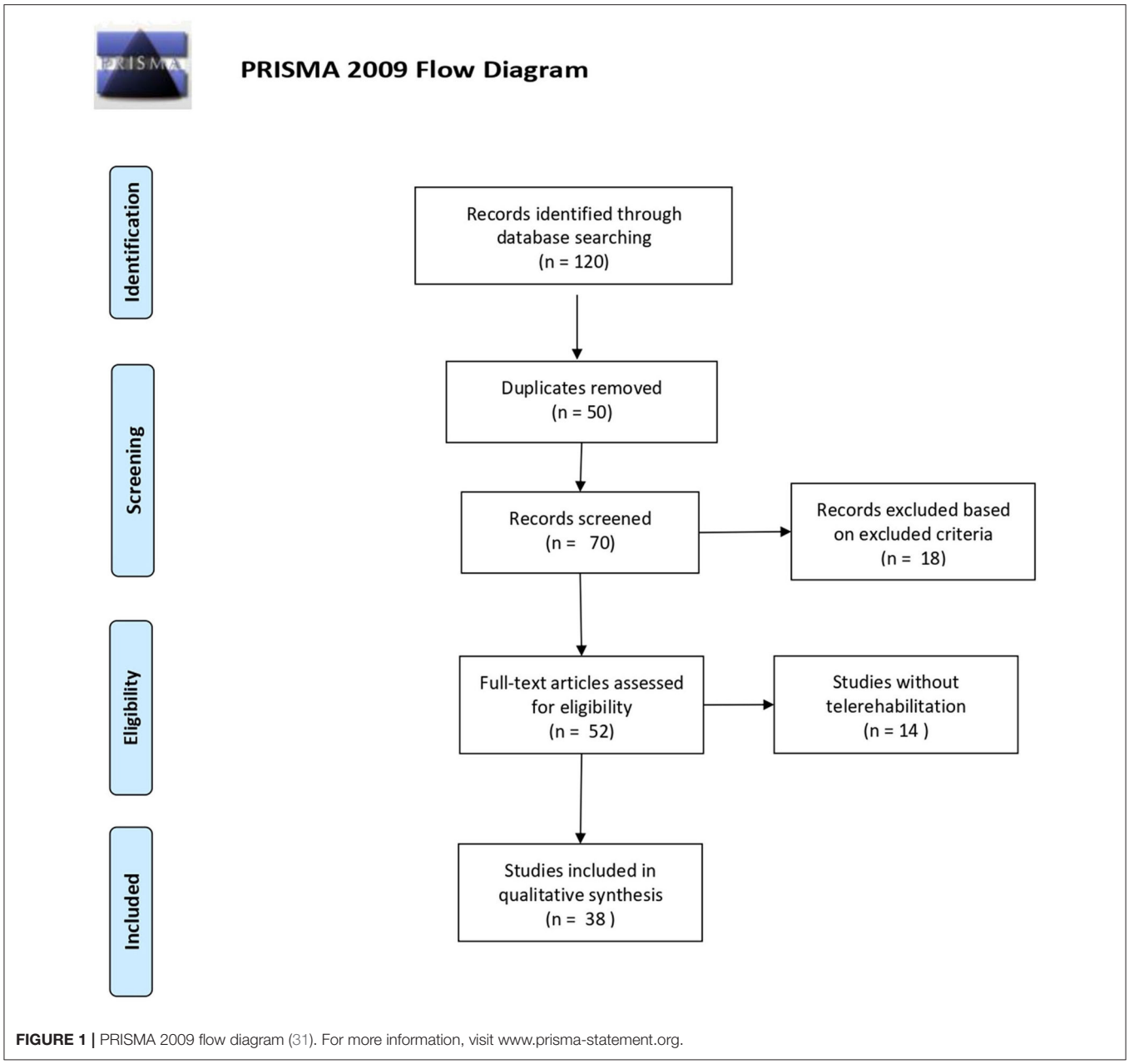

FIGURE 1 | PRISMA 2009 flow diagram (31). For more information, visit www.prisma-statement.org.

telerehabilitation studies for the treatment of the motor function of the upper limb after stroke confirmed these data. Despite these promising results, it is still unclear whether telerehabilitation in the motor field can be effective in neurological patients.

Postural Control and Falls

Few studies have been carried out in Italy to evaluate falls in a multifactorial way and to develop risk management programs (24, 32). Giordano et al. (24) performed a RCT to evaluate the effects of a home intervention program delivered by a multidisciplinary health-care team on older people, showing the positive effects of this home program. Barnocchi et al. (32) carried out a fall prevention program conducted by a remote physiotherapist on 283 elderly patients. The telerehabilitation program included home physiotherapy training on strength, balance, walking, and a weekly monitoring call by the nurse. The authors observed that their 6-month integrated program was feasible and effective in preventing falls in elderly with chronic diseases and at high risk of falling (32).

Other telerehabilitation studies on postural control have concerned patients with Parkinson's disease (PD) (33). Commonly, this patient population has motor disorders (i.e., up to 75% of people with PD) with postural instability, gait and balance deficits, and an increased risk of falls (48–52). Moreover, dopaminergic drugs have limited effects on postural instability in PD and rehabilitation is the most effective non-pharmacological

TABLE 1 | The main italian studies reporting either motor or cognitive outcomes following telerehabilitation.

	References	Sample	Major findings
TELEMOTOR REHABILITATION			
Postural control and falls	Giordano et al. (24)	145 EG/145 CG elderly patients	The authors performed a trial to evaluate the effects of a home intervention program delivered by a multidisciplinary health-care team on *older people*. The results showed positive effects of the home program.
	Bernocchi et al. (32)	141 EG/142 CG elderly patients	The authors carried out a telerehabilitation program to prevent fall and they observed that their 6-month integrated program was feasible and effective in preventing falls in elderly with chronic diseases and at high risk of falling.
	Gandolfi et al. (33)	38 EG/38CG PD patients	The study evaluate the effects of a remote rehabilitation training on balance, mobility, quality of life, frequency of fall in patients with PD. The authors observed that static and dynamic postural control was improved more in the PD patients receiving VR-based balance training at home.
	Carpinella et al. (34)	21 EG/21 CG PD patients	The study shows the feasibility and efficacy of a new system, the GAMEPAD (GAMing Experience in Parkinson's Disease) for the biofeedback rehabilitation of balance and gait in PD.
	Isernia et al. (35)	30 PD, 32 SM and 45 stroke patients	The authors proposed a motor and cognitive rehabilitation program, the Human Empowerment Aging and Disability (HEAD), and they found that a telehealth approach is both feasible and effective in providing rehabilitation care, ensuring continuity of care and encouraging the autonomy of daily life.
Upper limb	Piron et al. (16)	36 stroke patients	This work found that subjects with post-stroke upper limb deficits exposed to telerehabilitation treatment in a virtual environment could obtain moderately better motor performance than conventional therapy.
	Sgandurra et al. (36)	12 EG/12 CG UCP children	The results of this study showed that telerehabilitation could be promising in upper limb recovery in children with unilateral cerebral palsy (UCP).
	Dallolio et al. (37)	90 EG/90 CG SCI patients	The authors show that in patients with spinal cord injury, motor telerehabilitation would persist over time. Thus, the tool may offer benefits to patients discharged compared to standard treatments in terms of improving functionality.
TELECOGNITIVE REHABILITATION			
Pediatric neurological disorders	Corti et al. (38)	32 adolescents adolescents with brain damage	The authors observe that home cognitive telerehabilitation can be very useful in adolescents with congenital or acquired brain damage and with various levels of cognitive functioning.
	Pecini et al. (39)	34 children with Dyslexia	The authors found that rapid automatized naming (RAN) could be a valid tool in children with reading difficulties to empower the cognitive processes underlying reading, implement of intensive, specific, and early interventions, reduce costs for the healthcare system and long waiting lists.
	Simone et al. (40)	16 SM and 40 ADHD children	The study underline the efficacy of a home-based computerized-program for retraining attention. Data suggest that a cognitive rehabilitation program that targets attention is a suitable tool for improving global cognitive functioning in these patients.
Neurological diseases in adulthood	Torrisi et al. (41)	20 EG/20CG post-stroke patients	This work show effectiveness of a virtual reality telerehabilitation system to improve cognitive functioning in 40 post-stroke patients, thanks to a tablet connected remotely with clinicians.
	Maresca et al. (42)	15 EG/15 CG patient with post-stroke aphasia	The authors demonstrate effectiveness of a specific home telerehabilitation program for post-stroke aphasia, using a virtual reality touch-screen tablet.
Neurodegenerative diseases	De Luca et al. (43)	10 EG/10 CG patients with dementia	The study demonstrate that web-based cognitive rehabilitation can be useful in improving cognitive performance, besides psychological well-being, in demented individuals living in home care.
	Realdon et al. (44)	15 EG/15 CG MCI and AD patients	This work showed the effectiveness of a telerehabilitation and telemonitoring home assistance service of MCI and AD patients, to preserve cognitive and motor functioning and increase autonomy in daily life.
	Fabbri et al. (45)	30 EG/30 CG MCI and VCI (vascular cognitive impairment) patients	Results of this study underline on the efficacy of the proposed telerehabilitation to prevent or delay further cognitive decline in MCI/VCI subjects. Indeed, this tool could be promising to counteract cognitive decline and improve both physical functioning and quality of life.
	Dobbs et al. (46)	16 PD patients	The authors created a remotely supervised tDCS protocol for PD patients, combined with cognitive rehabilitation; This protocol allowed the PD patients to receive treatment at home, with reduction of fatigue and improvement of cognitive functioning.
	Alloni et al. (47)	45 neurological patients	The authors propose a tool, CoRe, for cognitive rehabilitation and they underline the importance of support systems for therapists in the provision of remote services, which allow the involvement and participation of users.

treatment to reduce the risk of falls (53). However, the growing disability, geographic distances and irregular distribution of rehabilitation services can hinder access to care services for PD patients (54). Given that virtual reality (VR) telerehabilitation has proven feasible and effective in improving various neurological conditions (55, 56), Gandolfi et al. (33) conducted a comparative study assessing the effects of either a standard rehabilitation program or a remote rehabilitation training on balance, mobility, quality of life, frequency of fall in patients with PD. The authors observed that static and dynamic postural control was improved more in the PD patients receiving VR-based balance training at home. On the contrary, the improvements in mobility and balance were greater in those who received conventional rehabilitation. Furthermore, confidence in the performance of outpatient activities, speed of gait, reduction of falls and a better quality of life were positively perceived by all of the patients, independently from the treatment.

Carpinella et al. (34) sought to investigate the feasibility and efficacy of a new system, the GAMEPAD (GAMing Experience in Parkinson's Disease) for the biofeedback rehabilitation of balance and gait in PD. The authors observed that the training was feasible and more effective than traditional physiotherapy on gait performance and the results were maintained for about 1 month. The same positive results were also obtained by Isernia et al. (35), who proposed a motor and cognitive rehabilitation program, the Human Empowerment Aging and Disability (HEAD), on 30 PD patients, 32 individuals with multiple sclerosis (MS) and 45 patients with chronic stroke. The authors found that a telehealth approach is both feasible and effective in providing rehabilitation care, ensuring continuity of care and encouraging the autonomy of daily life (35).

Upper Limb

In their interesting work, Piron et al. (57) provided five post-stroke patients with a motor telerehabilitation therapy based on increased feedback, suggesting that telerehabilitation could promote learning of the arm's motor skills away from the healthcare facilities, with reduced healthcare costs. In fact, another work by the same authors, carried out on a sample of 36 patients with post-stroke upper limb deficits, found that subjects exposed to telerehabilitation treatment in a virtual environment could obtain moderately better motor performance than conventional therapy (16). These results confirmed the previous pioneeristic study, which was conducted on a smaller group of patients with post-stroke motor deficits, who underwent a motor telerehabilitation program with promising results (6). Taken together, these findings demonstrate that telerehabilitation could be a simple method to treat stroke motor disorders, and could favor hospital discharge.

More recently, other studies have focused on demonstrating the effects of motor tele-rehabilitation in developmental disorders. Sgandurra et al. (36) applied a rehabilitation approach, called UPper Limb Children Action Observation Training, based on action observation training, showing that telerehabilitation can be promising in upper limb recovery in children with unilateral cerebral palsy.

Although several studies have shown that telerehabilitation is effective in improving motor outcomes in different neurological populations, the conclusive evidence on the efficacy of telerehabilitation for the treatment of motor function, regardless of the pathology, has not been reached. However, a positive effect was found for patients following orthopedic surgery, stroke, PD and in the elderly, suggesting that the increased intensity provided by telerehabilitation is a good option to be offered to the patients (23). Furthermore, as observed by Dallolio et al. (37) in patients with spinal cord injury, the results of telerehabilitation would persist over time. Thus, the tool may offer benefits to patients after discharge, as compared to standard treatments, in terms of improving functionality, although more studies are needed to advance the neurological field.

TELE-COGNITIVE-REHABILITATION

Neuropsychological rehabilitation stimulates cognitive functions to achieve the patient's maximum degree of autonomy and independence. Cognitive rehabilitation therapy has been defined as systematic and functionally oriented therapeutic cognitive activities directed to achieve functional changes by reestablishing or strengthening previously learned patterns of behavior or establishing new patterns of cognitive activity or compensatory mechanisms for impaired neurological systems. Thus, similar to the other types of rehabilitation therapy, cognitive rehabilitation includes both restorative and compensatory approaches. Cognitive rehab may be provided in a traditional way (i.e., the paper and pencil approach) or using innovation technology. There are various cognitive rehabilitation software, with different characteristics, such as the ability to adapt the level of difficulty of the exercises to the patient's performance and to choose sets of exercises based on the patient's deficit (58, 59). In the last decades, advances in ICT have led to the development of platforms and applications to enable patients' cognitive rehabilitation therapy at home. A crucial role is played by the professional and his/her abilities to involve the patients in their treatment process.

Rosso et al. (60) designed a platform based on the principles of cognitive rehabilitation and operators' decision-making. The latter has proven very important, as it affects the treatment by personalizing the exercises, the settings of cognitive exercises, and feedback.

Cognitive telerehabilitation has been used in the treatment of different neurological conditions and to improve different cognitive domains.

Pediatric Neurological Disorders

Technology-based treatments represent a promising field for multidisciplinary rehabilitation of children with acquired brain injury (ABI). Corti et al. (22) underlined in a recent review that telerehabilitation is promising to enhance cognitive and behavioral domains remotely. Traditional cognitive rehabilitation is known to have some limitations related to the time, costs, and accessibility of patients to these services (61–63). Therefore, the use of rehabilitation technology could also allow the provision of services remotely and in a non-medical environment (61, 64).

Zampolini et al. (61) have found that telemedicine allows for continuity of care in the treatment of neurodevelopmental disorders, limiting the time and economic needs of families and institutions. It also allows for precise monitoring of patient performance through online monitoring. Indeed, in another study, Corti et al. (38) investigated the feasibility of home computerized cognitive training in a group of 32 subjects aged between 11 and 16 years, observing that home cognitive training can be very useful in adolescents with congenital or acquired brain damage and with various levels of cognitive functioning.

Another field of application of cognitive telerehabilitation in developmental age is dyslexia. Pecini et al. (39) compared a training (Reading Trainer) working on the reading impairment with one [Run the rapid automatized naming (RAN)] working on the RAN impairment. The authors found that RAN could be a valid tool in children with reading difficulties by passing the use of alphanumeric stimuli, but empowering the cognitive processes underlying reading. This aspect could be useful for the implementation of intensive, specific, and early interventions, which in the traditional approach entail a series of complications, such as high costs for the healthcare system, long waiting lists that often lead to delayed treatments (65–67). In another study by the same authors on transparent spellings, it was found that software for a home-rehabilitation of reading disorders in children with dyslexia can involve the different linguistic, visual, and attentional processes, and integrate the components into a complex activity, such as reading (68). According to these studies, various authors (65, 68–71) have observed that telerehabilitation can be a promising approach potentially affecting multiple cognitive and linguistic components at the basis of normal and compromised reading, given that dyslexia has a "multifunctional deficit model." Thus, it is believed that ICT can effectively speed up reading aloud after only a few months, and this can facilitate the automation of reading processes (65, 68).

In fact, the home telerehabilitation software allows intensive and daily interventions, and the levels of difficulties and settings are managed by the operator to improve the automation process (72, 73), inserting activities with the difficulty of the exercise above the performance of the child, making the task not only stimulating but also easy to guarantee success (74). In addition, the adaptation of the intervention also allows continuous feedback to the child and stimulates greater self-control of competence (75–77).

Finally, recent applications of telerehabilitation in pediatric age have been aimed at the treatment of cognitive deficits in pediatric-onset multiple sclerosis (POMS) and in children with attention deficit hyperactivity disorder (ADHD). In fact, Simone et al. (40) performed a pilot study on these pediatric populations to evaluate the effectiveness of a home computerized attention program. The authors found that the tool was useful for improving overall cognitive functioning in patients with POMS, but it had a minor effect in patients with ADHD.

Neurological Diseases in Adulthood

Stroke is a leading cause of mortality in industrialized countries (78), as well as the leading cause of long-term disability in adults. The prevalence of post-stroke cognitive dysfunction ranges from 23 to 55% within 3 months of the stroke onset, and decreases between 11 and 31% after 1 year (79–81). The main post-stroke cognitive deficits involve attention and concentration (82), memory (83), spatial awareness (84), perception (85), praxis (86), and executive functioning (87), with a significant reduction in autonomy of daily life and quality of life. In recent years, VR tele-rehabilitation has been used to manage this patient population, with the aim of reducing healthcare costs and encouraging continuity of care. A recent study (41) has evaluated the effectiveness of a VR telerehabilitation system to improve cognitive functioning in 40 post-stroke patients. After an initial training phase, the patients continued rehabilitation at home thanks to a tablet, connected remotely with clinicians. Data showed the effectiveness of telerehabilitation for the treatment of cognitive disorders following stroke, with an improvement in global cognitive functioning, attentional processes, verbal fluency, short-term memory and mood. These results seem promising for the management of cognitive disorders in stroke patients, through continuity of care that allows maintenance of the recovery achieved, as well as to reduce hospitalizations and improve the patient's emotions and well-being (41).

Almost 30% of patients with ischemic and hemorrhagic stroke have an aphasic syndrome in the acute phase (88–90), and when severe, aphasia may persist all lifelong. Aphasia has a significantly negative impact on well-being, independence, social participation, quality of life, and it is often associated with severe depression (91, 92). Early therapy is important for promoting language recovery, which is essential for daily communication and social participation (26). Maresca et al. (42) assessed the effectiveness of a specific home telerehabilitation program for post-stroke aphasia, using a VR rehabilitation system touch-screen tablet in 30 patients. The study showed that telerehabilitation could be one solution for the treatment of aphasic patients after discharge, by promoting the continuity of care, monitoring results, and improving linguistic abilities, mood and psychological well-being.

Another area of the application of telerehabilitation in the stroke field concerns visual impairments, with regard to hemianopia, which may affect cognitive functioning and neurological recovery (93). In fact, the presence of visual defects can be very debilitating and interfere with daily life, negatively affecting the prognosis of stroke and the independence of the person, with a significant negative emotional impact and social implications. Tinelli et al. (94) developed an audiovisual telerehabilitation system, based on the brain's multisensory ability, in order to provide a new tool to improve eye movements toward the blind half-field. This tool has been tested on three adult patients, leading to improvements in visual detection skills with long-term effects. Therefore, the results showed that in stroke, telerehabilitation could be a promising, convenient and accessible tool for more patients, relieving the NHS (94). In addition, remote rehabilitation allows intense and prolonged intervention for patients who may not be able to access the healthcare system.

The potential of telerehabilitation could be confirmed by Calabrò et al. (95), who are conducting a multicenter

study on the role of cognitive telerehabilitation in individuals with ABI, evaluating the functional recovery of patients, psychological well-being, the burden of caregivers with a cost-effectiveness analysis.

Neurodegenerative Diseases

Another neurological field of increasing interest for telerehabilitation concerns neurodegenerative diseases, also considering the limited efficacy of drugs in these pathologies. According to the World Alzheimer Report (96), dementia affects 46.8 million people worldwide, with an increasing burden on society and the families. The lack of drugs that can stop or slow the course of the disease have encouraged non-pharmacological approaches for people with/at risk of dementia, such as in Alzheimer Diseases (AD), Mild Cognitive Impairment (MCI), Frontotemporal Dementia (FTD), and PD. De Luca et al. (43) assessed the effectiveness of cognitive training on 20 people with dementia living in a nursing home, observing that web-based cognitive rehabilitation can be useful for improving cognitive performance, as well as psychological well-being. Similar results were obtained by Cotelli et al. (97), who showed that cognitive telerehabilitation interventions have the same efficacy as face-to-face rehabilitation in patients with MCI, AD and FTD. Moreover, Realdon et al. (44) showed the efficacy of a telerehabilitation and telemonitoring home assistance service to preserve cognitive and motor functioning and increase autonomy in daily life in 30 MCI and AD patients. New research is taking place to evaluate the effectiveness of telerehabilitation in preventing or delaying further cognitive decline and improving physical functioning and quality of life (44, 45).

As for PD, recent studies have observed that telerehabilitation allows the delivery of combined treatments involving cognitive stimulation and transcranial direct current stimulation (tDCS). The latter is a non-invasive brain stimulation technique that has been shown to improve several symptoms of neurological disorders, such as depressed mood, fatigue, motor deficits and cognitive dysfunction. Dobbs et al. (46) created a remotely supervised tDCS (RS-tDCS) protocol for PD patients to increase accessibility of this tool, reducing the burden on physician, patient and caregiver. RS-tDCS combined with cognitive rehabilitation was feasible, and it allowed the PD patients to receive treatment at home, with consequent reduction of fatigue and improvement of cognitive functioning. Hence, according to the authors (46), RS-tDCS after-effects can be generalized to provide tDCS for home rehabilitation to patients with other neurological disorders, including multiple sclerosis (MS).

MS is a chronic immune-mediated disease of the central nervous system, and it is a major cause of disability in young adults. The disease can lead to motor, sensory, cognitive and behavioral anomalies, and recently there has been a growing interest in the development of innovative rehabilitation treatments, even outside the hospital environment. Di Tella et al. (98), in their systematic review and meta-analysis, evaluated the effectiveness of integrated telerehabilitation on motor, cognitive and participation outcomes in people with MS. The authors reported that MS patients may benefit from motor telerehabilitation, but have low cognitive and participation outcomes. Further research is needed to confirm the results and develop integrated systems that allow addressing the user's multiple requests. For this reason, Alloni et al. (47) proposed a tool, i.e., the CoRe, for cognitive rehabilitation of a variety of diseases, customizing the exercises according to the preferences and performance of the patients. The authors underlined the importance of specific support systems for therapists in the provision of remote services, which allow the involvement and participation of the users (47).

TELEMONITORING, TELEASSISTANCE, AND BEYOND

Home telemonitoring of chronic diseases is a promising approach that provides accurate and reliable patient's data, influencing attitudes and behaviors toward daily life, potentially improving his/her medical conditions (99). In recent years, various studies have encouraged the use of remote monitoring for chronic diseases at home. Neuromuscular diseases (NMD) present with progressive muscle deficits, with consequent loss of walking, difficulty swallowing and weakness of the respiratory muscles, and such disorders deserve a continuous follow up.

Portaro et al. (100) carried out a study to evaluate the effectiveness of telemedicine in monitoring 4 patients with facio-scapulo-humeral dystrophy (FSHD), a hereditary disease characterized by variable and asymmetrical involvement of the muscles of the face, trunk, upper and lower limbs. The patients had a severe form of FSHD (with chronic respiratory failure) and lived on a small island (Lipari, Sicily), far away from the treatment center. The authors pointed out that the telemonitoring system was simple to use, efficient and effective for home management of these patients with FSHD, and allowed reduction of hospitalizations.

Another interesting study was conducted by Trucco et al. (101), for the home management through telemedicine of adult patients with a ventilator-dependent NMD. The 2-year longitudinal multicenter study found that telemedicine was effective in improving home management of respiratory exacerbations in the young patients, and it was overall well-tolerated.

Also, telemonitoring has been found effective in other chronic neurological conditions. Marzianiak et al. (102) observed the effects of telemonitoring *via* an e-Health app in MS patients. The authors pointed out that this app can improve predicted outcomes, access to treatment as well as disease information. In particular, it has been found that the e-Health app has allowed an active participation in all aspects of the self-management of the pathology, including the control of adherence to treatment, changes in bladder and bowel habits, activities of daily live and mood. According to the authors, telemonitoring devices may be important in the management of chronic diseases, such as MS, to simplify the multidisciplinary approach (102). These tools could facilitate

remote monitoring of symptoms, adverse events and patient outcomes, and might allow efficient use of resources and limit the time spent in hospital, permitting a more timely intervention of scheduled face-to-face visits. Moreover, telemedicine can also be a useful approach for assistance of elderly with chronic diseases. Maresca et al. (20) treated 22 elderly patients with a multidisciplinary telemedicine approach to improve their quality of life. The authors observed that tele-assistance could be an effective care tool for the elderly, promoting remission of depressive symptoms and improving social functioning, cognitive levels and eating habits, helping in preventing the exacerbations of pre-existing chronic diseases. In fact, another work by the same authors (103) suggested that telemedicine (telemonitoring/teleassistance) could be useful to improve health and quality of life of disadvantaged elderly people, suffering from severe comorbidity or living far from health services. Moreover, patients reported high levels of satisfaction with the service, although the system was not easy to use (103).

In a systematic review performed by Nordio et al. (104), it has been observed that tele-rehabilitation improves the patient's adherence to the treatment. High levels of satisfaction and adherence to telemedicine treatment were found also by Piron et al. (11) in post-stroke patients. These works reinforce the hypothesis that remote services are a feasible alternative to standard care (11, 18). Other authors have highlighted the advantages of telemedicine, especially of tele-rehabilitation services, such as reducing costs (both for public health and for patients) and increasing the access to care for patients living in isolated areas, where traditional rehabilitation services may not be easily accessible (24, 69).

However, Perretti et al. (105) found that the patients were skeptical about the efficacy of a therapy mediated by a telemedical system (pc, videoconferencing) without a direct and vis-a-vis interaction with the healthcare professionals. For this reason, the authors suggest both a monitoring patient feedback (to adapt rehabilitation techniques and approaches to his/her needs), and the need for adequate training of the users involved. In line with these authors, Calvaresi et al. (106) made a focus group with physiotherapy and telerehabilitation experts, identifying as the strength of an appropriate approach the possibility of (i) contextualizing the scenario, (ii) promptly solving planning and problem-solving uncertainties, and (iii) offering reliable sources of information and controls. In addition to these proven positive characteristics, limitations were found, such as incompatibility with real-time operating systems, and inability to perform interventions in integrated devices (106). For this reason, new and larger studies are needed to demonstrate the positive effects and evaluate the strengths and limitations of telemedicine in the rehab field.

ONGOING PROJECTS AND FUTURE PERSPECTIVES

Currently, in Italy, some health care centers use telerehabilitation for provision of health services. In particular, Bramanti et al. illustrated an ICT model implemented in Sicily to ensure the continuity of care, which is very difficult because of the geographical characteristics and socio-economic problems of the island. In fact, the IRCCS Centro Neurolesi "Bonino-Pulejo" of Messina, together with the Sicilian Government and the Ministry of Health, has incorporated the telehealth system into the long-term post-stroke patient care program to provide continuous rehabilitation and reduce disability (8). The project follows a hub-and-spoke system, consisting of a main supplier center (hub) integrated by secondary institutions (spokes), that offer more limited services. Patients are followed during their individual rehabilitation path (from intensive rehabilitation to home rehabilitation). Through a system of telerehabilitation with virtual reality (i.e., the Virtual Reality Rehabilitation System—VRRS, Khymeia, Italy, shown in **Figure 2**), patients are treated with specific programmed exercises, which are continuously modified according to the individual cognitive and motor state. VRRS is a virtual reality system that allows telerehabilitation. VRRS is used in two ways (i) online, with a live interaction between the patient and the therapist *via* videoconference and (ii) offline, in which the patient performs the exercises remotely with the help of a virtual assistant, while the therapist can view results later (8).

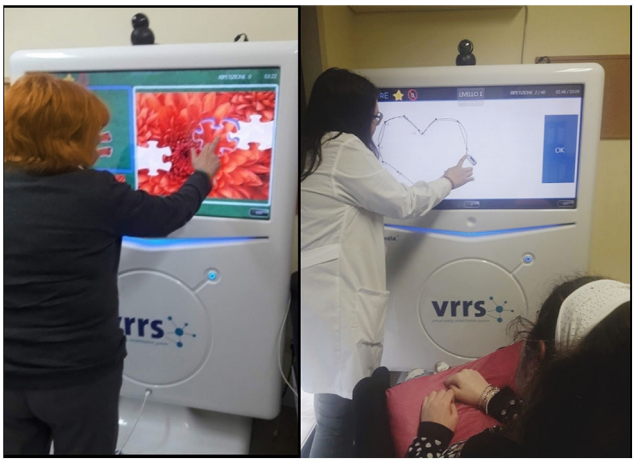

FIGURE 2 | The VRRS system: the Italian Telerehab tool used for both motor and cognitive rehabilitation.

Following this positive experience, the Italian Ministry of Health founded in 2015 a National Telerehabilitation network involving the main Research Institutes (i.e., the "Istituti di Ricovero e Cura a Carattere Scientifico," IRCCS) and aimed at assessing the efficacy and cost-effectives analysis of telerehab in the treatment of different neurological disorders, including stroke, dementia, PD, and MS. Also, Calabrò et al. (107) underlined the potential of telemedicine in guaranteeing distance training and comparison between the healthcare professionals, encouraging the relationship between the Hub center and the Spokes. In fact, these centers are constantly connected thanks to telemedicine: the different specialists support each other, both for diagnosis and for rehabilitation. Furthermore, this program

allows the application of standard protocols with fairer and uniform health services (107).

AUTHORS' POINT OF VIEW AND CONCLUSIONS

We could hypothesize that telemedicine services, when used correctly, can contribute to a transformation of the healthcare sector and business models. Telemedicine can assist in an early and protected hospital discharge, which is nowadays necessary because of the increase in life expectancy, and the increase in chronic and post-acute illnesses. Moreover, telerehabilitation can be useful to avoid a direct contact between clinicians and patients, and this issue is of outmost importance during pandemics, like COVID-19 is (108).

For this reason, information technologies applied to medical science can be useful in countering today's socio-health problems. The analysis of Italian telemedicine studies and projects shows that they have led to satisfactory results and have provided solutions to hitherto unresolved problems. Unfortunately, the samples of these studies are small, thus making the results not very relevant for a substantial economic analysis. Specifically, studies on telerehabilitation suggest that it is not yet widely disseminated, despite scientific results are increasingly suggesting its effectiveness. One of the reasons may be the difficulty of creating software suitable for a remote therapeutic setting. In fact, flexible devices that are adaptable to different types of deficits and ample connectivity are needed to better reach users at home. For this reason, the effectiveness of telerehabilitation services compared to standard care is still under debate. All the research on telerehabilitation considered in this study highlights the need to standardize the procedures, purposes and targets that characterize this therapeutic modality. However, considering the growing burden of care and the need to provide adequate and continuous services to chronic patients, telerehabilitation is becoming an interesting and promising model of care. To understand if the infrastructures can be adequate for carrying out such rehabilitation services, valid tests must be designed and carried out to avoid wasting resources and inconclusive results.

Future telerehabilitation studies should include cost responsibility and cost-effectiveness analysis associated with clinical outcomes.

In conclusion, according to the Italian experience with telemedicine applied to the neurorehab field, the studies of this review support the development of telerehabilitation, but the quality of research needs to be significantly improved to clarify benefits and risks of remote assistance. Studies, protocols and guidelines about teleneurorehabilitation are needed from all over the world in order to share the different experiences and better assess the cost-effectiveness analysis of this promising tool, potentially improving healthcare services, especially during pandemics.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Written informed consent was obtained from the individuals for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

RC, GM, MM, and PT: substantial contributions to the conception and design of the work, interpretation of data, revising the work critically for important intellectual content, final approval of the version to be published, and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. RD, AM, and LP: acquisition and analysis of data, drafting the work, final approval of the version to be published, and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors contributed to the article and approved the submitted version.

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The Application of Lexical Retrieval Training in Tablet-Based Speech-Language Intervention

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In the setting of shortened hospitalization periods, periods of confinement and social isolation, limited resources, and accessibility, technology can be leveraged to enhance opportunities for rehabilitative care (1). In the current manuscript, we focus on the use of tablet-based rehabilitation for individuals with aphasia, a language disorder that frequently arises post-stroke. Aphasia treatment that targets naming through effortful and errorful instances of lexical retrieval, where corrective feedback is generated on every trial, may enhance retention and generalizability of gains (2, 3). This pilot evaluation explored how six individuals with aphasia interacted with a tablet-based therapy application that targeted lexical retrieval. Participants with aphasia either (1) autonomously engaged with the therapy tasks or (2) received systematic encouragement to effortfully retrieve words. Behaviors of response latency and cue use were examined to gain insights into the behavioral patterns of both groups, as well as analyses of task accuracy and outcomes on standardized cognitive–linguistic assessments. Despite some variability, initial observations suggest that participants who received systematic training refrained from using cues to complete tasks and spent longer on each trial, which ultimately co-occurred with increased independent engagement with therapy and improved standardized outcomes. Preliminary results present an alternative means of leveraging technology to implement best-practice recommendations in the context of aphasia telerehabilitation.

Keywords: telepractice, aphasia, lexical retrieval training, effortful learning, technology

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INTRODUCTION

Technology-based teletherapies for aphasia are increasingly utilized in outpatient treatment as treatment of this type bypasses barriers imposed by financial, geographical, and temporal access (4, 5). Beyond circumventing these constraints, such therapies can be leveraged to increase the intensity of treatment as they are accessible from any setting at any time (1, 6–12). Furthermore, even when therapy is administered remotely, clinicians are able to monitor progress and tailor therapy to a client's unique needs (4, 5, 8, 13–15). Recent work by Kiran et al. (16) demonstrated that utilizing tablet-based language rehabilitation can simultaneously increase the intensity of practice while also tailoring treatment to the individual participant's needs. Furthermore, work by Godlove et al. (14) suggests that the environment in which tablet-based therapy is administered (home vs. clinical context) does not impact the extent to which naming gains are incurred.

However, gaps in the literature about the behaviors that people with aphasia (PWA) develop when engaging with tablet-based therapies remain (17–20). The effectiveness of tablet-based therapy is rooted in a person's ability to integrate and learn from the individual treatment tasks; however, little is known about how individuals with aphasia go about navigating and learning from technologically based interventions independently.

Studies of lexical retrieval are increasingly evaluating cue use, success, and effort, the results of which suggest that effortful and successful lexical retrieval promote the greater gains in naming (2, 3, 21, 22). Effortful treatment conditions for aphasia provide therapy participants the opportunity to make errors and receive feedback on performance accuracy (3, 23), such as through the presentation of visuals, sounds, verbal cues, or other clinician or tablet-based actions.

Such effortful conditions are often described as errorful therapy, as individuals are made aware of their errors, and have been found to be particularly beneficial in naming rehabilitation as they call the individual to draw information from long-term memory (3, 21, 22). Furthermore, there is evidence that the practice of autonomously retrieving a stimulus name, even when incorrect, improves treatment outcomes (2, 22–25). Moreover, greater long-term retention is observed particularly in conditions of effort, consistent with the principle that repeated retrieval practice improves access to stored information (2, 3, 22). Feedback on trial accuracy is often provided in the context of errorful tablet-based therapies, but what remains to be established is how patients engage with, learn from, and manage the feedback provided by the applications.

An essential aspect of effortful, errorful, and repeated lexical treatment practice is that it calls upon the individual to self-monitor and self-correct his or her choices (26), heightening the engagement of the individual client and enhancing long-term gains. A study by Pyc and Rawson (27) found a relationship between long-term retention and increased target retrieval time, where increased response times were interpreted as a reflection of increased effort. This is consistent with the findings by Schwartz et al. (26): the more a patient self-monitors and exerts effort to retrieve a response, the more time he or she will take to give a response.

However, past literature suggests that certain PWA do not develop strategies to effectively manage feedback-based instruction (28). Cognitive deficits are increasingly being identified in aphasia (29–36) spanning the domains of attention, memory, executive function, language, and visuospatial skills (29, 33, 36–45). Impairments in these domains might influence the way that PWA independently approach treatment that taps into effortful lexical retrieval practice. For example, Villard and Kiran (35) suggest that attention, or the lack thereof, can greatly influence not only the naming performance but also the language treatment outcomes. Furthermore, the importance of the quality, in addition to the quantity of practice, cannot be overlooked in evaluating treatment (46, 47). While a frequent and well-spaced dosage of treatment is necessary for improvement (3, 12), the quality of treatment, as shaped by speech therapist input and client output (24), must be considered. As rehabilitation demands requirement for tablet-based applications to become increasingly utilized within and *as* therapy, it is essential to explore (1) the ways in which PWA independently engage with technologically based telepractice for naming rehabilitation and (2) the ways in which behavioral training can serve to improve the quality of independent practice.

Apart from being corrective, the feedback provided in tablet-based naming therapy can include the possibility of pre-response cues: visual and/or auditory features that provide further information about a particular stimulus before a response is selected. As such, users can self-administer cues to either find out or verify an answer. Des Roches et al. (19) found that there are distinct profiles of cue use in people who participate in tablet-based language treatment and that the self-administration of cues may relate to aphasia severity: more severe patients tended to use more cues. The authors' findings highlighted two dichotomized profiles of cue use, (1) participants who had higher performance accuracy with increased cue use and (2) participants who had lower performance accuracy with increased cue use [(19), p. 11], suggesting that independent engagement with therapy is user-dependent and not always effective.

Therefore, the current pilot study aimed (1) to observe the behaviors of people independently engaging with a tablet-based application and (2) to pilot a protocol that taught individuals ways to enhance lexical retrieval attempts in both home and clinical environments of therapy. To accomplish this, we investigated the effect of a 10-week lexical retrieval protocol on participant behaviors of response latency, proportion of cue use, independent engagement with the treatment, and task accuracy. The protocol examined in the current work looks at ways to apply best research evidence into clinical practice that is supported by technology to promote enhanced outcomes. We hypothesized that lexical retrieval training could be used to teach PWA to increase autonomous effortful lexical retrieval attempts in tablet-based language rehabilitation targeting word finding. Successful adherence to the trained protocol was predicted to lead to a delayed response selection and a reduced cue use, as both of these behaviors were trained throughout treatment. Therefore, we predicted that individuals who received training would have a longer response and use a lower proportion of cue use and that these behaviors would not differ by location. As longer latencies and reduced cue use are likely to reflect the kind of independent and effortful lexico-semantic processing that is described in studies that examine errorful learning (2, 3, 22, 23), individuals who received training were hypothesized to have greater accuracy on treatment items and standardized assessments of naming.

MATERIALS AND METHODS

Participants

The participants in this study included six adults with chronic post-stroke aphasia (four males and two females, mean age = 62.3, SD = 6.72) and were recruited through the MGH Institute of Health Professions Aphasia Center and *via* word of mouth. The Institutional Review Board (IRB) research consent form was reviewed with each participant and individuals provided informed consent prior to the initiation of the study. In order to be eligible, individuals had to have

aphasia and be in the chronic stages of aphasia at least 6 months post-onset. Five of the participants had aphasia subsequent to left hemisphere strokes, whereas the aphasia of one participant (Trained 1) was related to a left hemisphere tumor resection. Participants had to be between the ages of 18 and 85 years and pre-morbidly right-handed English speakers with no history of significant psychiatric or medical disease. Participants also had to demonstrate impairments in naming ability as demonstrated on the Boston Naming Test (BNT) (48), the Naming and Word Finding subtests of the Revised Western Aphasia Battery (WAB-R) (49), and patient interview (see **Table 1**).

In order to be eligible, participants had to achieve a minimum score of 70% on the auditory comprehension subtests of the WAB-R (including yes/no questions, auditory word recognition, and sequential commands), as multiple therapy tasks required attending to spoken instructions and/or spoken stimulus items. The presence of a field cut as determined by the Cognitive and Linguistic Quick Test (50) symbol cancellation task would render participants ineligible as this could interfere with the ability to look at all portions of the iPad screen. As part of their first intervention session, the participants were taught to log in to the therapy application, make button responses, and turn the iPad on and off. Participants were provided with a printed handbook of instructions on these tasks and with contact information of the research team to help with any technical difficulties. This informal instruction period also served as a screen to ensure that the participants could meet the study participation demands of logging into the application and making button presses on the touch screen. In a follow-up to this pilot study, our lab has developed an iPad navigation screening and teaching tool to more formally evaluate baseline abilities to perform tasks on an iPad and/or learn to perform tasks on an iPad (51).

Procedure

All the participants were involved in a 10-week treatment study that used a tablet-based language therapy application, Constant Therapy, a research-based language rehabilitation program devised by researchers at Boston University that incorporates tasks to address many domains of language and has been used in research studies investigating aphasia rehabilitation (Constant Therapy, Inc., Newton, MA, USA) (14, 15, 44, 52). Constant Therapy was selected because it allows for the tracking of response latency, cue use, and response accuracy, measures that enabled us to evaluate behaviors both in the clinic and during home practice. Participants were pseudo-randomly assigned to the Untrained group, where they would independently engage with therapy, or the Trained group, where they would receive training targeting effortful lexical retrieval. The three participants in the Untrained group had diagnostic profiles of anomic, Broca's, and transcortical motor aphasia. Of the three participants assigned to the Trained group, all had diagnoses of anomic aphasia. While the distribution of diagnoses across groups was initially more balanced, two additional participants initially enrolled in the study discontinued their participation shortly after consent.

Pre- and Posttreatment Assessments

All the participants completed standardized pre- and posttreatment assessments to measure cognitive and linguistic ability, the 60-item BNT (48), the WAB-R [WAB; (49)], and the CLQT (50). Posttreatment assessments were administered by study staff who were blinded to group assignment. Due to scheduling conflicts, this was not the case for participant Trained 1, whose posttreatment assessment had to be completed by the final author and did not include the BNT.

Experimental Tasks

The experimental tasks used in our treatment protocol were selected from the tablet-based Constant Therapy treatment application (4, 16) based on their effectiveness in targeting anomia and the limited task demands on reading. Furthermore, the selected tasks fell into one of two categories of either requiring or not requiring the covert or silent retrieval of a target word to successfully complete a trial. The tasks utilized in this study were category matching (CM), feature matching (FM), rhyming (RH), and syllable identification (SI). For each analyzed task, the picture of a noun appeared on screen accompanied by a spoken task prompt, written feature, or category, and participants made a response *via* screen touch. Nouns represented a wide variety of semantic categories, including but not limited to animals, furniture, body parts, and clothing. CM and FM engaged participants in considering the category membership of an item or the semantic features associated with a pictured item. In CM, the participants were instructed to select the correct category from a choice of three. In FM, the participants were instructed to press "Yes" or "No" to indicate whether an item had a feature or not (e.g., pictured item: banana, feature "has legs"). During the CM and FM tasks, lexical–semantic representations are thought to be improved through a strengthening of the feature and category associations with the target (53–56). Retrieval of the target word form was not necessary to perform the tasks.

In contrast, the RH and SI tasks required the covert retrieval of the exact word form of a pictured target to make an informed response for each trial. In RH, the participants were asked to indicate whether the name of a pictured target item rhymed with a spoken target item (e.g., pictured item: pen, spoken target "Does this rhyme with hen?"). For SI, the participants were asked to indicate whether the name of a pictured item had two syllables. For both the RH and SI, the participants indicated their response by selecting "Yes" or "No." Participants could also press a button to hear the task prompt repeated.

For all tasks, a small audio icon in the upper corner of the picture target offered the opportunity to hear the name of the pictured item. We refer to this option as the *cue*, and participants in the Trained group were encouraged to refrain from using this cue button that provided the target word form until they had attempted to retrieve the target name independently (see details of training below). We anticipated that participants would show a reduced tendency to use the cue button on the CM and FM tasks, where the word form was not necessary to complete the task. In contrast, prior work with PWA completing the RH and SI tasks suggested that participants might exhibit a tendency for immediate and frequent use of the cue button to hear the target

TABLE 1 | Profiles of the patients enrolled in the 10-week protocol.

Participant	Age (years)	Chronicity of stroke (years)	Aphasia diagnosis	Memory[a]	Attention[a]	Executive function[a]	Visuospatial ability[a]	WAB-R AQ: pre	WAB-R AQ: post	WAB-R NWF[b]: pre	WAB-R NWF[b]: post	BNT: pre	BNT: post
Trained 1	64.9	9.5	Anomic	152, mild	140, mild	8, severe	53, mild	75.4	79.1	60	80	33	41
Trained 2	69.7	3.5	Anomic	143, moderate	156, mild	20, mild	79, mild	77.8	86	63	81	26	39
Trained 3	68.8	11.7	Anomic	191, mild	205, WNL	26, WNL	95, WNL	69.9	76.7	56	66	20	32
Untrained 1	52.3	8.06	Broca's	60, severe	185, WNL	24, WNL	102, WNL	33.8	41.8	31	31	19	NA
Untrained 2	59.9	29.0	TCM	123, moderate	184, WNL	24, moderate	92, WNL	67.7	68.2	92	95	51	55
Untrained 3	58.3	5.1	Anomic	125, moderate	187, WNL	28, WNL	92, WNL	89.5	89.2	64	65	16	15

WAB-R, Western Aphasia Battery - Revised; AQ, Aphasia Quotient; BNT, Boston Naming Test; WNL, within normal limits.
All columns marked with "a" indicate that these are subtests of the Cognitive Linguistic Quick Test (50). All columns marked with "b" indicate that they are derived from the WAB-R.

word since retrieving its word form was necessary to complete a trial. For all task trials, the participants received feedback related to their response accuracy in the form of a green check or a red "X" accompanied by a chime or a discrete buzz before proceeding to the next item. The application was programmed to present 15 trials of each task before moving on to the next. In the version of Constant Therapy available at the time of the study, item selection and presentation schedule (repeated vs. unique items) cannot be controlled by the clinician; therefore, the participants saw a mix of unique and repeated items.

Trained vs. Untrained Therapy

Each participant was provided with an iPad that had access to Constant Therapy. All the participants attended 2 h of in-house therapy sessions at the MGH Institute of Health Professions Aphasia Center. Although a standardized assessment of reliability of treatment administration was not computed, each session was observed by either the first or the last author to assess the accuracy of protocol administration (on which feedback was provided following the session). Additionally, all the participants were encouraged to independently complete the assigned therapy program tasks once a day from home. At the start of each clinic session, clinicians reviewed the login frequency with each participant based on the following protocol:

1. I see that you logged in *X* times since I last saw you.
   a. If logins are daily: I'm glad to see that you're using the app frequently.
   b. If logins are infrequent: I see that you didn't log in very much. What happened?
2. Did you have any trouble using the iPad or logging in to Constant Therapy?
3. Is there any task that you feel is particularly difficult?

Afterwards, clinicians asked the participants to log in to Constant Therapy to complete their task battery. Participants in the Untrained group, as the name suggests, completed all of the Constant Therapy tasks independently. During the clinic sessions, clinicians scored the performance and observed how patients naturally interacted with the therapy application. Clinicians were allowed to provide simple clarification of task instructions and had scripts that provided them with acceptable ways to review the definition of a rhyme and a syllable (see **Supplementary Materials** for the task-specific protocol instructions that the Trained group received). Beyond instruction and keyword clarifications, clinicians were not allowed to provide additional semantic information, cues, or response guidance. If the Untrained participants asked questions or solicited additional feedback, clinicians were instructed to encourage participants to "make your best response" and to complete the tasks independently.

For the Trained group, the focus of in-clinic sessions was to (a) encourage lexical retrieval attempts on every trial of each task and (b) teach participants to review responses after receiving incorrect feedback. After clinicians assessed the login frequency of each participant, the participants were asked to log in to the Constant Therapy application. Then, clinicians instructed the participants to: "try to name every item that you see" on every task trial. Clinicians reminded the participants that the cue button, when pressed, would state the pictured item name. Participants were informed that they should *not* press the cue button until they had tried to retrieve the name and responded to the trial. Following this instruction, if the participants made attempts to select the cue button, the clinicians would stop the participant, stating, "Wait, I want you to think of the name first. Make your best guess and listen to the name after." If participants selected the cue, clinicians prompted them to repeat the name after listening to it. Anytime feedback from the application indicated that a response was incorrect, the participants were instructed to pause, reflect upon their answer, and review the correct response before moving on to the next trial. Furthermore, clinicians encouraged participants to use these strategies when practicing tasks independently at home (see **Supplementary Materials**).

This overt lexical retrieval protocol was based on the principle that effortful lexical retrieval attempts and independent engagement with therapy can improve naming (3, 22). The protocol was also designed to include components that could be reliably measured and tracked throughout the course of therapy both in-house and during independent home practice in a realistic manner for clinicians: response latency, cue use before response selection, trials completed per login, and accuracy. Furthermore, this protocol was applied to tasks that either did or did not require the overt verbalization of a lexical item. Adherence to the protocol was expected to lead to increased response latencies and a reduced proportion of cues, and that these behaviors would carry over to home practice. The metrics of latency and cue use were automatically tracked by Constant

TABLE 2 | Mean latency, cue use, trials, and accuracy for CM+FM and RH+SI for both the Untrained and Trained groups by time point.

Task	Group	Location	Week	Latency	SE	Cue use	SE	Trials/Login	SE	ACC	SE
CM+FM	Trained	Clinic	1	15.04	6.22	0.30	0.30	27.8	10.8	0.79	0.06
			10	16.12	8.59	0.00	0.01	19.0	5.43	0.90	0.03
		Home	1	9.97	3.15	0.15	0.18	41.7	16.5	0.79	0.07
			10	10.83	1.19	0.00	0.00	20.0	0.00	0.88	0.03
	Untrained	Clinic	1	12.02	5.34	0.48	0.28	47.9	24.9	0.81	0.11
			8	9.04	4.10	0.27	0.16	40.0	15.9	0.82	0.02
		Home	1	7.22	1.53	0.26	0.22	24.8	8.15	0.77	0.10
			8	4.26	0.62	0.03	0.04	12.3	3.18	0.68	0.02
RH+SI	Trained	Clinic	1	18.33	12.73	0.87	0.60	27.1	12.9	0.81	0.05
			10	7.10	0.16	0.68	0.23	30.0	0.00	0.47	0.03
		Home	1	18.1	18.49	0.59	0.54	41.1	16.7	0.69	0.04
			10	17.7	5.79	0.20	0.20	21.8	3.40	0.68	0.03
	Untrained	Clinic	1	11.9	2.89	0.94	0.43	48.1	25.3	0.73	0.08
			10	9.77	1.68	1.39	0.13	27.0	14.0	0.75	0.03
		Home	1	10.9	5.08	0.93	0.43	24.8	8.4	0.63	0.01
			10	6.79	0.98	0.99	0.32	15.0	0.73	0.68	0.02

CM+FM, category matching + feature matching; RH+SI, rhyming + syllable identification; ACC, accuracy.

Therapy and therefore provided a means of inferring protocol application during home-based logins.

Analysis

The Constant Therapy application collected and tracked data and thus generated reports that included measures of login times, response selection accuracy, response latency time, number of cue requests, and latency before cue selection. Based on the dates listed in the output, we were able to calculate the total number of days the participants logged into treatment at home. Data from a total of 36,464 trials was accrued over the duration of the study. Trials with response latencies 3 standard deviations above the mean (by participant) were excluded from analyses as these were unrepresentative of overall behavior and indicated an interruption to therapy (as the application did not time out on its own if a participant ended a login mid-trial). Of the remaining 34,688 trials, we measured the intensity of treatment by calculating the total number of unique login (averaging across home and clinical practice), as well as the average number of trials per login per week, for each participant. Then, we calculated the following measures by unique participant login by task: (1) the average latency (in seconds) before a response was selected in a trial; (2) the average proportion of cues (playing audio recordings of the pictured item names) selected before a response per trial; (3) the number of trials completed; and (4) the average accuracy.

We used linear mixed-effects models for our regression analyses to estimate the extent to which factors of group (Trained vs. Untrained), location (clinic vs. home), and time (days) explained the outcomes on measures of response latency, cue use before response selection, trials per login (intensity), and accuracy measured throughout the course of treatment [e.g., utilizing the linear mixed-effects model (fixed = Measure ∼ Group*Location*Time, reStruct = (1|Participant), data = datafile, method = "REML"] (57). In our model, the participant variable was designated as the random effects. Since the requirements for lexical retrieval differed by task type, data for the CM and FM tasks (CM+FM) and the RH and SI tasks (RH+SI) were respectively grouped together in analyses. Figures for behaviors of latency and cue use separated by each task are available in **Appendices B, C**. We analyzed our measures of interest within and across groups and therapy contexts in order to investigate the impact of the training protocol and whether this protocol would carry over to home practice. We used Tukey's *post-hoc* tests to further interpret significant interaction effects from our linear mixed-effects regressions. We also calculated the number of unique logins each participant completed.

To probe for generalized improvement, we report on changes between the pre- and post-assessment scores and use the benchmarks proposed in Gilmore et al. (58) for the WAB-R Aphasia Quotient (AQ) and BNT. Additionally, to account for the heterogeneity of the baseline scores within and between groups, we examined item-level improvement on the WAB-R (Aphasia Quotient composite score, Naming and Word Finding subtest) and BNT in every individual participant by computing Marx and Cummings' (59) normalized change scores. Normalized change (*c*) scores differ from change scores (post – pre) as they allow us to determine the overall level of improvement someone demonstrates on a measure relative to their baseline performance and the maximum possible change in score. Following the protocol detailed in Marx and Cummings (59), *c* scores were calculated as POST – PRE/MAXIMUM POSSIBLE SCORE – PRE; if a participant demonstrated a loss, the calculation was POST – PRE/PRE, and if there was no change, the score was 0. Finally, we calculated the percentage of treatment items that each participant saw that overlapped with items on the WAB-R and the BNT. Analyses were conducted utilizing R version 1.2.1335. Mixed-effects regressions were conducted utilizing lme4 (57) and plots were generated using ggplot2 (60).

TABLE 3 | Results from the mixed-effects linear model analyses examining the relationship of group (factor; trained vs. untrained), location (factor; clinic vs. home), and *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$.

Measure	Task	Parameter	Estimate	95% CI: Upper	95% CI: Lower	SE	*t*	*p*
Latency	CM+FM	(Intercept)	16.2	20.4	12.0	2.12	7.65	<0.0001
		Untrained	−8.97	−2.97	−14.9	3.06	−2.93	0.004**
		Home	−3.75	1.07	−8.57	2.46	−1.53	0.128
		Time	−0.04	0.06	−0.14	0.05	−0.94	0.347
		Untrained × Home	2.09	9.36	−5.18	3.71	0.56	0.574
		Untrained × Time	0.21	0.37	0.05	0.08	2.65	0.008**
		Home × Time	0.12	0.22	0.02	0.05	2.41	0.017*
		Untrained × Home × Time	−0.25	−0.07	−0.43	0.09	−2.88	0.004**
	RH+SI	(Intercept)	39.3	54.3	24.3	7.67	5.13	<0.001
		Untrained	−39.7	−15.4	−64.0	12.4	−3.20	0.002**
		Home	12.2	29.4	−5.05	8.80	1.38	0.168
		Time	−0.28	0.03	−0.59	0.16	−1.76	0.079
		Untrained × Home	−1.83	25.4	−29.1	13.9	−0.13	0.896
		Untrained × Time	0.67	1.16	0.18	0.25	2.63	0.009**
		Home × Time	−0.19	0.16	−0.54	0.18	−1.06	0.289
		Untrained × Home × Time	−0.17	0.38	−0.72	0.28	−0.62	0.534
Cue use	CM+FM	(Intercept)	0.23	0.31	0.15	0.04	5.08	<0.001
		Untrained	0.17	0.29	0.05	0.06	2.64	0.009**
		Home	−0.09	0.01	−0.19	0.05	−1.74	0.083
		Time	0.00	0.00	0.00	0.00	−2.54	0.011*
		Untrained × Home	−0.11	0.03	−0.25	0.07	−1.34	0.180
		Untrained × Time	0.00	0.00	0.00	0.00	−1.00	0.318
		Home × Time	0.00	0.00	0.00	0.00	1.37	0.173
		Untrained × Home × Time	0.00	0.00	0.00	0.00	0.41	0.680
	RH+SI	(Intercept)	0.00	0.43	−0.43	0.22	−0.01	0.989
		Untrained	1.79	2.49	1.08	0.36	4.95	<0.001****
		Home	0.44	0.95	−0.07	0.26	1.71	0.089
		Time	0.01	4.62	−4.59	0.00	2.35	0.019*
		Untrained × Home	−0.46	0.34	−1.26	0.41	−1.11	0.266
		Untrained × Time	−0.03	−0.01	−0.05	0.01	−3.34	<0.001***
		Home × Time	−0.01	0.01	−0.03	0.01	−2.36	0.019*
		Untrained × Home × Time	0.02	0.04	0.00	0.01	1.97	0.049*
Trials/Login	CM+FM	(Intercept)	43.5	51.6	35.3	4.16	10.5	<0.001
		Untrained	−0.81	10.9	−12.6	5.99	−0.13	0.893
		Home	4.44	13.9	−5.03	4.83	0.92	0.359
		Time	−0.08	0.09	−0.26	0.09	−0.89	0.375
		Untrained × Home	−25.0	−10.7	−39.3	7.28	−3.44	<0.001***
		Untrained × Time	−0.01	0.28	−0.30	0.15	−0.09	0.931
		Home × Time	−0.15	0.05	−0.35	0.10	−1.54	0.124
		Untrained × Home × Time	0.17			0.17	0.97	0.333
	RH+SI	(Intercept)	40.1	48.5	31.7	4.29	9.35	<0.001
		Untrained	1.58	13.5	−10.4	6.09	0.26	0.796
		Home	5.25	15.7	−5.16	5.31	0.99	0.323
		Time	−0.07	0.11	−0.25	0.09	−0.71	0.475
		Untrained × Home	−25.6	−10.6	−40.6	7.63	−3.36	<0.001***
		Untrained × Time	−0.06	0.23	−0.35	0.15	−0.38	0.706
		Home × Time	−0.18	0.06	−0.42	0.12	−1.55	0.122
		Untrained × Home × Time	0.25	0.60	−0.10	0.18	1.37	0.172
Accuracy	CM+FM	(Intercept)	0.78	0.84	0.72	0.03	578.6	<0.001

(Continued)

TABLE 3 | Continued

Measure	Task	Parameter	Estimate	95% CI: Upper	95% CI: Lower	SE	*t*	*p*
		Untrained	0.02	0.16	−0.12	0.07	0.06	0.814
		Home	0.02	0.08	−0.04	0.03	0.35	0.551
		Time	0.00	0.00	0.00	0.00	3.02	0.082
		Untrained × Home	−0.02	0.04	−0.08	0.03	0.49	0.485
		Untrained × Time	0.00	0.00	0.00	0.00	0.30	0.583
		Home × Time	0.00	0.00	0.00	0.00	5.34	0.021*
		Untrained × Home × Time	0.00	0.00	0.00	0.00	4.23	0.040*
	RH+SI	(Intercept)	0.77	0.83	0.71	0.03	22.2	<0.001
		Untrained	−0.07	0.03	−0.17	0.05	−1.32	0.186
		Home	−0.07	0.01	−0.15	0.04	−1.52	0.129
		Time	0.00	0.00	0.00	0.00	−2.18	0.030*
		Untrained × Home	−0.06	0.06	−0.18	0.06	−1.02	0.306
		Untrained × Time	0.00	0.00	0.00	0.00	2.13	0.034*
		Home × Time	0.00	0.00	0.00	0.00	1.41	0.159
		Untrained × Home × Time	0.00	0.00	0.00	0.00	−0.69	0.493

CM+FM, category matching + feature matching; RH+SI, rhyming + syllable identification. Time (continuous; days).

RESULTS

Behavioral means and standard errors of response latency, proportion cue use, trials per login, and accuracy were computed for all task types and are reported in **Table 2** for reference. Participant-specific means are reported in **Appendix A**. Means are reported for the first week of participation (excluding the first clinic session as the participants were unfamiliar with the therapy tasks and protocol) and the final week of intervention to reflect patterns of behaviors by group in the initial and final stages of treatment.

Latency

The linear mixed-effects regression results demonstrate a main effect of group, with the Trained group showing longer response times on CM+FM ($p = 0.004$) and RH+SI ($p = 0.002$) task types (see **Table 3**). There were no main effects of location or time. The interaction of group and time was significant for both CM+FM ($p = 0.008$) and RH+SI ($p = 0.009$).

For CM+FM, additional interactions of location and time ($p = 0.017$), where the response latencies were longer at home, and group, location, and time ($p = 0.004$) were significant (see **Figure 1** and **Tables 2**, **3**). Tukey's *post-hoc* tests demonstrated that on CM+FM in clinic, the Trained group took longer than the Untrained group on days 1–49 at $p < 0.05$. Beginning on day 63, the Untrained group took significantly longer on the CM+FM treatment task trials than did the Trained group in clinic ($p < 0.001$). The Trained group took significantly longer at home through treatment between all days 1–70 at $p < 0.05$. On RH+SI, the Trained group took significantly longer in clinic between days 1–2 and 8–49. Between days 63 and 65, the Untrained group took significantly longer on trials in clinic at $p < 0.01$. The Trained group took significantly longer on the RH+SI task trials at home at $p < 0.05$ between days 8 and 70.

Cue Use Before Response Selection

The main effect of group was significant for cue use on CM+FM ($p = 0.009$) and RH+SI ($p < 0.0001$; see **Figure 2**), where the Untrained group used a higher proportion of cues per trial than did the Trained group. There was no significant main effect of location for either task type. The main effect of time was significant for CM+FM ($p = 0.011$), where cue use went down over time for all groups. While the main effect of time was also significant for RH+SI, the reverse happened and cue use increased over time ($p = 0.019$). There were no significant interactions of group, location, and time for CM+FM. For RH+SI, there were significant interactions of location and time ($p = 0.19$), group and time ($p < 0.001$), and group, location, and time ($p = 0.049$; see **Figure 2**). Tukey's *post-hoc* tests revealed that the Untrained group used significantly more cues than did the Trained group on CM+FM at $p < 0.05$ in clinic between days 12 and 41 and at home between days 7 and 55. On RH+SI, the Trained group used significantly fewer cues at $p < 0.05$ between days 8 and 59 in clinic and between days 2 and 70 at home.

Trials per Login (Intensity) and Logins

There were no significant main effects of group, location, or time for CM+FM or RH+SI. The interaction of group and location was significant for both CM+FM ($p < 0.001$) and RH+SI ($p < 0.001$), where the Trained group completed significantly more trials per login at home than did the Untrained group (see **Figure 3**). By the end of treatment, the Untrained group completed an average of 37 unique logins (SE = 6.37) and the Trained group averaged 50 (SE = 9.42), as averaged across locations.

Accuracy

While there were no main effects of group, location, or time for CM+FM, for RH+SI, there was a significant main effect

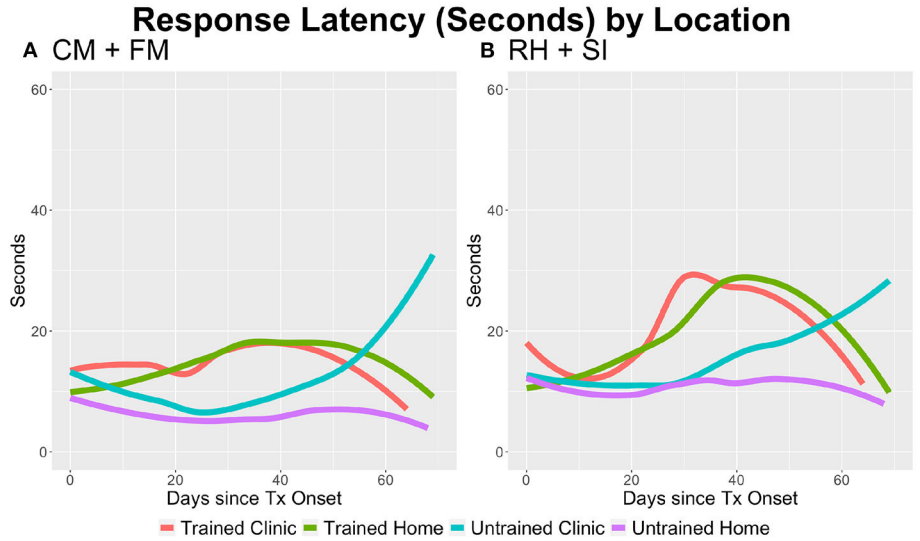

FIGURE 1 | The average response latency per trial by task type, group, and location. **(A)** On category matching + feature matching (CM+FM), the Trained group took longer per trial ($p = 0.002$) and over time in the home setting ($p = 0.004$). The Untrained group took longer over time ($p = 0.008$), and all participants took longer in the home setting ($p = 0.017$). **(B)** On rhyming + syllable identification (RH+SI), the Trained group took longer per trial ($p = 0.002$) and the Untrained group took longer over time ($p = 0.009$).

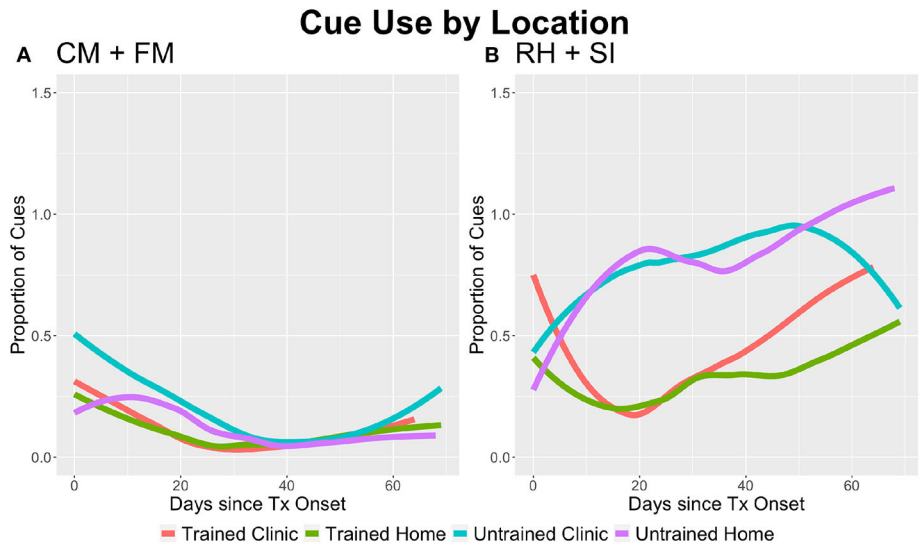

FIGURE 2 | The average proportion of cues used per trial by task type, group, and location. **(A)** On category matching + feature matching (CM+FM), the Trained group used a lower proportion of cues per trial ($p = 0.009$) and all groups used less cues over time ($p = 0.011$). **(B)** For rhyming + syllable identification (RH+SI), the Trained group used less cues than the Untrained group ($p < 0.001$); however, the Untrained group used less cues over time ($p < 0.001$), but more cues than the Trained group over time during independent practice at home ($p = 0.049$). For all participants, cue use increased overall over time ($p = 0.019$), but decreased in the home setting ($p = 0.019$) as treatment progressed, suggesting that cue use in clinic increased.

of time ($p = 0.030$), with accuracy decreasing over time, the effect driven by clinic performance for the Trained group and home performance for the Untrained group (see **Figure 4**). The interaction of location and time ($p = 0.021$) was significant for CM+FM, with home accuracy being lower than clinic accuracy in the early third of therapy and becoming more similar as therapy progressed. The interaction of group, location, and time ($p = 0.04$) was also significant for CM+FM, where the Trained group performed similarly in clinic and at home in the early phases of therapy, where scores in the final third of therapy were higher at home than in clinic. For the Untrained group, accuracy was lower at home than in clinic in the early phases of therapy and showed the opposite pattern late in therapy. Furthermore, Tukey's *post-hoc* testing demonstrated that the Trained group

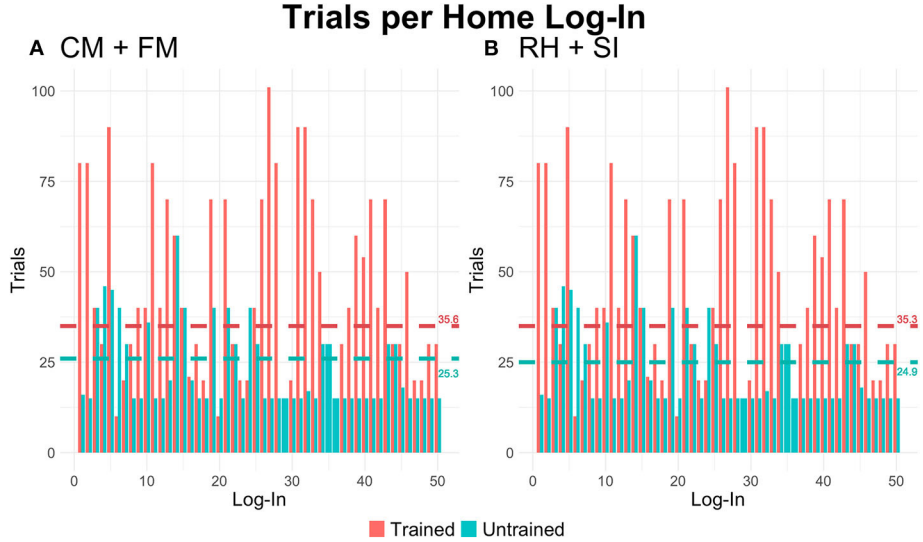

FIGURE 3 | The average number of trials per unique login by task type and group during independent home practice. *Horizontal lines* represent the average number of trials completed per login by group (*teal*: Untrained). **(A)** For category matching + feature matching (CM+FM), the Untrained group completed significantly fewer trials at home than the Trained group ($p < 0.001$). **(B)** Consistent with behaviors reported for CM+FM, Untrained participants completed significantly fewer trials during independent practice at home on the rhyming + syllable identification (RH+SI) tasks ($p < 0.001$).

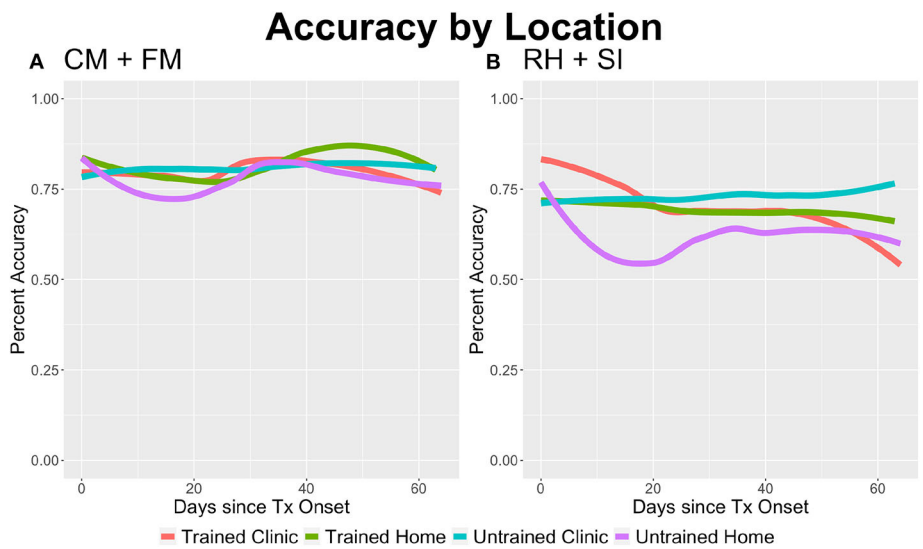

FIGURE 4 | The average accuracy on trials by task type, group, and location. **(A)** All participants achieved higher accuracies during independent practice at home on category matching + feature matching (CM+FM) ($p = 0.021$); additionally, the Untrained group achieved higher accuracies at home over time ($p = 0.040$). **(B)** All participants improved their performance over time on rhyming + syllable identification (RH+SI) ($p = 0.030$), where the Untrained group made greater gains on treatment items over time ($p = 0.034$).

performed higher at home than did the Untrained group between days 1 and 56 on CM+FM at $p < 0.05$. For RH+SI, the interaction of group and time was significant ($p = 0.034$), where Tukey's *post-hoc* testing demonstrated that the Untrained group performed significantly higher than the Trained group in clinic at $p < 0.05$ between days 21 and 70, but significantly lower than the Trained group at home at $p < 0.05$ between day s 8 and 69.

Standardized Assessment Outcomes

Two of the Trained participants and one Untrained participant met the Gilmore et al. (58) 5.03 benchmark of significant change on the WAB-R AQ. Similarly, all three Trained participants but only one Untrained participant (Untrained 2) met the 3.30 benchmark of significant change on the BNT. All three Trained participants achieved normalized gains with small to medium effects (one medium) on the WAB-R AQ, WAB-R Naming

TABLE 4 | Change scores and Marx and Cummings' (2007) normalized gain scores on standardized assessments of language.

Assessment	Group		Pre-treatment scores	Post-treatment scores	Change scores	*c* scores
WAB-R AQ	Trained	1	75.4	79.1	3.70	0.15
		2	77.8	86	8.20	0.38
		3	69.9	76.7	6.80	0.23
	Untrained	1	33.8	41.8	8.00	0.12
		2	67.7	68.2	0.50	0.02
		3	89.5	89.2	−0.30	−0.03
WAB-R NWF	Trained	1	60.0	80.0	20.0	0.50
		2	63.0	81.0	18.0	0.49
		3	56.0	66.0	10.0	0.23
	Untrained	1	31.0	31.0	0.00	0.00
		2	92.0	95.0	3.00	0.37
		3	64.0	65.0	1.00	0.03
BNT	Trained	1	33.0	41.0	8.00	0.30
		2	36.0	39.0	13.0	0.38
		3	20.0	32.0	12.00	0.30
	Untrained	1	19.0	NA	NA	NA
		2	51.0	55.0	4.00	0.44
		3	16.0	15.0	−1.00	−0.02

For the interpretation of results, c scores below 0.30 are considered to have a low effect, scores between 0.30 and 0.70 medium effect, and scores above 0.70 a large effect (59, 61). WAB-R, Revised Western Aphasia Battery; BNT, Boston Naming Test.

and Word Finding subtest (two medium), and BNT (three medium). In the Untrained group, one participant achieved normalized gain with small effect on the WAB-R AQ, whereas another made gains with medium effect on both the WAB-R Naming and Word Finding subtest and the BNT (see **Table 4** and **Figure 5**). We also calculated the percentage of items that participants saw throughout the course of treatment that were also on the WAB-R and BNT. For CM+FM, 2.37–4.06% (mean = 3.02, SE = 0.01) of the items the Trained participants saw were on the WAB-R and 5.99–7.53% were on the BNT (mean = 6.39, SE = 0.22). Similarly, for RH+SI, 1.52–2.37% (mean = 2.01, SE = 0.13) of the treatment items overlapped with items on the WAB-R and 5.32–7.29% on the BNT (mean = 5.40, SE = 0.2) for the Trained participants. For the Untrained participants, 1.88–2.71% of the treatment items overlapped with items on the WAB-R (mean = 2.49, SE = 0.20) and 5.27–8.78% on the BNT (mean = 6.38, SE = 0.31) on CM+FM. Finally, on RH+SI, 1.53–1.63% (mean = 1.56, SE = 0.20) of the items the Untrained participants saw overlapped with items on the WAB-R and 4.56–5.58% (mean = 5.26, SE = 0.28) on the BNT.

DISCUSSION

The current manuscript reports on a pilot study that aimed to examine and characterize behaviors of latency and cue use in individuals with aphasia engaged in tablet-based treatment for anomia. Tablet-based interventions are increasingly being utilized in aphasia rehabilitation with the goal of increasing patient access to therapy. Research is beginning to demonstrate the efficacy of tablet-based applications (4, 5, 8, 16). In the current work, our approach aimed to explore the untrained behaviors used by PWA while engaging in tablet-based anomia intervention and to evaluate these relative to the behaviors of PWA trained to delay response selection until independent lexical retrieval was attempted with a limited reliance on cues.

Therefore, the goals of this study were: firstly, to characterize PWA's behaviors during tablet-based treatment during independent completion of tasks; secondly, to see whether optimal behaviors (independent retrieval of lexical items without a reliance on cues) could be taught with strategy training; and thirdly, to see whether PWA would carry over the use of strategies at home without clinician presence and encouragement. Prior clinical experience with tablet-based intervention suggested that many PWA utilize cues provided by the application with little evidence of initiating lexical retrieval attempts independently (PWA have been observed to immediately request cues that verbalize the target item name and use this to inform their response), with little evidence of pausing on every trial and/or verbalizing item names. Therefore, the major focus of the protocol training was to direct individuals to attempt to retrieve a target lexical item before requesting cues integrated in the app, thereby applying principles intended to enhance gains during errorful intervention (3, 22, 26). Evaluating measures of response latency and the proportion of cues used tracked by the application allowed for an investigation of behaviors in both clinic and home settings accrued across the completion of many trials. Although the current sample size is small, the study was conducted within a realistic therapy context relevant to the current care process with intensive tracking of every individual trial each participant completed.

Our results suggest that training strategies to independently retrieve lexical targets and to acknowledge and review incorrect responses can alter and potentially improve PWA's engagement with teletherapy. We first examined the response latency and cue use, behaviors that were targeted by the training protocol. Across both task types, the Trained group took longer and used less cues than did the Untrained group. Furthermore, while there was an interaction of time and location for the Untrained group, the Trained group response latencies did not differ significantly by location. As predicted, cue use overall was lower for the CM+FM than the RH+SI tasks, where the former task type did not require the retrieval of word form to complete the therapy task. Even so, behaviors of latency and cue use differed between the Trained and Untrained group, suggesting that the strategy training influenced behaviors for tasks that did and did not require retrieval of the target word form. Strategy training in aphasia rehabilitation has primarily focused on teaching communicative partners strategies to support communication (62–64) and the training of augmentative or compensatory strategies to individuals with aphasia to assist the success and management of conversation (65–67). The preliminary results from our protocol suggest that individuals with aphasia are capable of learning strategies that

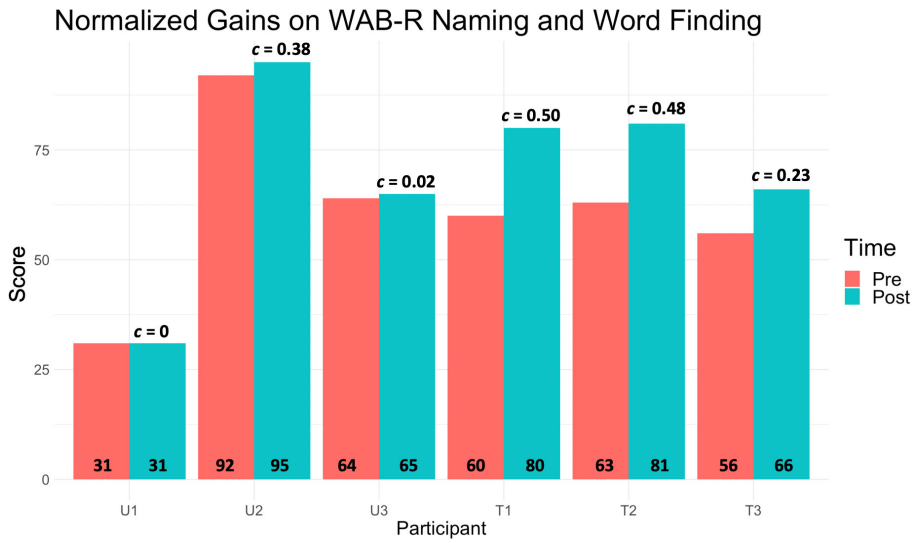

FIGURE 5 | The pre- (*orange*) and post- (*teal*) WAB-R Aphasia Quotient composite scores for each participant, where the normalized gain (*G*) scores are placed *above the corresponding bars* and raw pre- and post-scores *at the bottom of each*. All Trained participants' gain scores were close to medium effect posttreatment, whereas only one Untrained participant achieved the same.

aim to enhance the restoration of lexical retrieval and that the addition of these strategies to therapy targeting anomia may lead to greater naming gains. Furthermore, the preliminary finding that the application of strategy training led to greater generalized gains following restorative therapy motivates a reexamination of what providing restorative therapy, and ensuring the successful restoration of impaired or lost function, truly entails in the context of clinical practice, whether in person or *via* teletherapy.

We then examined the intensity of treatment as a measure of the number of trials completed per treatment login. For all tasks, the Trained group engaged more frequently (number of logins) and, furthermore, more intensely at home (number of trials per login) than did the Untrained group.

As all participants were encouraged to independently engage with the application as much as possible from home, a possible explanation is that the increased engagement of the clinician during the in-house clinic sessions for the Trained group relative to the Untrained group led to an increased motivation or attention of participants to continue to practice independently, though we acknowledge that other factors could also account for this difference. Prior research has shown that active engagement or strategy training can influence motivation and learning during rehabilitation (68–71). Skidmore et al. (71), for example, examined apathy, defined as the lack of motivation and interest, in 30 individuals from an in-patient stroke rehabilitation unit. All participants worked on four to six individualized rehabilitation goals throughout the study period, where 15 participants received additional strategy training to learn to self-evaluate and address goals through goal-setting, planning, and monitoring of performance. The researchers found that the strategy-trained group had lower scores of apathy and proposed that self-monitoring and problem solving may have promoted participant perseverance and engagement. Metacognitive training similarly teaches self-awareness and problem solving and has been thought to promote learning and motivation (68). Given these findings, the results of the current study are likely due to an increased monitoring of behaviors and self-evaluation that arose through the strategy training.

The average treatment task accuracy ranged from 67.2 to 78.7%, and accuracy on RH+SI actually decreased over time, driven by the Trained group's clinic performance. While cue use can assist a person to reach a correct response, the results suggest that task accuracy may not be the most important aspect of therapy. Prior work on retrieval practice has suggested that it is the combination of effortful retrieval and success that likely leads to the long-term benefits of learning conditions where the production of errors is not controlled (2, 3, 72). In conditions of learning where errors can occur, error detection or feedback is essential to support learning (26, 73–75). Constant Therapy tasks automatically offer feedback related to the accuracy of a response *via* visuals and audio, where the Trained group was additionally coached to press the cue button in the instance of negative feedback in order to hear the name of the target item and support the integration of learning. Importantly, as hypothesized, behaviors of increased latency and reduced cue use prior to response selection led to improved generalized outcomes.

Improvements on standardized assessment outcomes (WAB-R and BNT) were observed, where the Trained group more successfully met the benchmarks proposed in Gilmore et al. (58) and achieved higher normalized gains. The findings support prior work identifying superior outcomes in settings of effortful lexical retrieval (2, 3, 21, 22). The findings are also likely influenced by the increased number of logins and trials completed. One participant in the Untrained group (Untrained 2) improved on

the Naming and Word Finding subtest of the WAB-R as well as the BNT. Interestingly, this participant self-developed strategies through the course of therapy. Of note is that this participant had a high naming ability as measured by the BNT and WAB-R at baseline, which may also explain why his accuracy on the treatment items did not change significantly over time. He was included in this study as he does present with anomia and describes this deficit as being a barrier in his communication. While his pretreatment performance was high, it is notable that he was still able to make gains, which may be attributable to the strategies he self-developed throughout the course of treatment. By the end of the study, by his own initiative, this participant wrote down any target for which he was uncertain of the response and documented the feedback provided by the app. This resulted in long delays before responding and drove many of the effects seen wherein the Untrained group showed increasing latencies of response in the final weeks of therapy (see **Appendix A** for individual participant means). The observation of this type of behavior is consistent with prior work examining cue use that determined that autonomous user engagement with therapy is variable (19). Some PWA may naturally develop strategies that support optimal engagement with tablet-based therapy applications, while others may benefit from training to better support their practice.

The findings provide encouraging pilot evidence to suggest that training can lead to increased lexical retrieval attempts and reduced cue use and, furthermore, that trained behaviors can be maintained from clinic to home practice. Furthermore, the intensive training of these behaviors appears to lead to increased autonomous engagement, as demonstrated by the increased intensity at which the Trained participants completed trials from home. The combination of increased response times, reduced cue use, and generalized treatment outcomes suggests that participants who spent more time per trial used this time to autonomously retrieve lexico-semantic information. If this change in cognitive process underlies the increased response times and reduced cue use, this theory, in addition to increased intensity, may explain why the Trained group demonstrated greater generalizable effects of treatment on standardized assessments of language, particularly the composite Aphasia Quotient of the WAB-R, and why the one individual of the Untrained group (Untrained 2) also improved. As such, as telepractice is increasingly utilized lieu of, or to support in-person treatment, it is essential to consider the role of the clinician in therapy and how clinic time can be spent training strategies that shape behaviors to promote outcomes or enhance engagement long term. Additional research will be needed to determine whether this is replicated and whether, as postulated, increased engagement of the clinician during clinic sessions promotes increased at-home practice.

Limitations

The current study was a pilot study to examine behaviors throughout tablet-based treatment and how these relate to outcomes on task performance and standardized assessments. The study had limitations, which we acknowledge, and must be taken into consideration when interpreting the results. First, data were collected from a small and variable sample. Within this small sample, group assignment was pseudo-randomized, and unfortunately two participants dropped out shortly after being consented, meaning that the groups that were not equally matched on language or cognitive ability (see **Table 1**). We hope to have compensated for this issue by utilizing normalized gain scores and published benchmarks of significance to examine within-participant gains on standardized assessments in a more objective way.

We chose to use a therapy platform that is widely available on tablets in order to make findings relevant and realistic to real-world clinical practice. In the version of Constant Therapy used at the time of treatment, however, specific items and the frequency at which items are represented cannot be controlled for; therefore, we were unable to track item-level improvement based on intensity of practice, and this brings a reduction in experimental control. Future directions of this work will be to implement a protocol where item-level improvement can be systematically monitored to examine the treatment-specific effects of practice in a controlled single-subject design. Despite its limitations, we put forward this protocol training and pilot results to demonstrate a unique way to envision the role of the clinician when working with PWA and tablet-based applications in light of reduced hospitalization times and limited access to rehabilitative care.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Mass General Brigham Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

RP, SP, and SV-R conducted all patient recruitment, experimental implementation, and gave substantial edits to the manuscript. SV-R is responsible for the experimental design. JG conducted all analyses and manuscript preparation. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.583246/full#supplementary-material

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CASE REPORT
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Integrated Discourse Therapy After Glioblastoma: A Case Report of Face-To-Face and Tele-NeuroRehabilitation Treatment Delivery

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Background: Language and communication impairments are among the most frequently reported long-term behavioral consequences of brain tumor. Such deficits may persist long after a patient has been discharged from the hospital and can significantly impact return to work, resumption of prior social roles, and interpersonal relations, as well as full engagement in leisure activities. While considerable research has centered on identifying and describing communication impairments in brain tumor survivors, relatively little research has investigated language therapy for this population.

Aims: This report (1) reviews the literature and describes the language and cognitive-communicative profile of a 35-year-old man 6 years post glioblastoma excision with subsequent chemo- and radiation therapies; (2) presents cognitive-communication outcome data for this individual following an integrated discourse therapy; and (3) assesses treatment feasibility in face-to-face (F2F) and tele-neurorehabilitation (TNR) contexts.

Methods: A battery of tests and weekly conversation probes were administered to evaluate baseline performance and potential changes associated with F2F and TNR treatment delivery. Integrated Conversation Therapy (ICT) was administered across four alternating (F2F and TNR) treatment blocks over 2 months. ICT is a solution-focused discourse intervention that simultaneously targets word finding, sentence processing, and authentic patient-selected conversational interactions.

Results: Although the participant presented with long term-language impairments that were clinically distinct from stroke-associated aphasia, statistically significant post-treatment gains (>2 SEM) were evident following F2F and TNR treatment delivery on standardized measures of apraxia, discourse production, verbal memory, and self-ratings of discourse production, communication, and living with aphasia. While objective measures of treatment effect size (probes of CIU discourse data) were consistent across F2F and TNR delivery models, results of a satisfaction survey indicated a slight but statistically significant participant preference for TNR treatment delivery.

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Conclusions: This study provides preliminary support for F2F and TNR delivery of ICT discourse intervention for glioblastoma survivors. It also highlights the need for more research specifically dedicated to language therapy for this population.

Keywords: tumor, telerehabilitation, aphasia, language, therapy, discourse, case report

INTRODUCTION

Studies report that at least 80% of BT survivors have cognitive and/or communication impairments at the time of initial diagnosis (1–6). These deficits can impact employment, social function, and overall quality of life long after patients have been discharged from the hospital (7–9). Literature reviews indicate that cognitive rehabilitation for BT survivors is feasible with the majority of individuals showing gains on measures of neuropsychological impairment (10–13), subjective ratings of cognitive function (11, 14), measures of independence (15, 16), and/or quality of life (17). Although this literature identifies language impairment as among the most common sequelae of brain tumor (6–8, 18), only a few studies have explicitly focused on language intervention. A recent review (19) identified several studies that provide preliminary evidence supporting language therapy for BT survivors. Some of these studies investigated broad rehabilitation outcomes and identified language/aphasia therapy as being a component of the program but did not provide specific details about the behavioral intervention (20–22). Other studies (23) focused on the language intervention but omitted key information associated with the medical history (e.g., tumor type/location) and/or biomedical treatments (e.g., chemotherapy, radiation). Only one study (23), targeting email use in individuals with severe cognitive impairment, included tele-neurorehabilitation (TNR) components (email with telephone follow-up).

This study adds a new case report of language TNR to this literature. BG, a glioblastoma survivor with a complex medical history and persistent non-fluent aphasia is unusual with respect to the extent of his initial tumor, the application of innovative chemotherapy, and his record of survivorship. Successful application of TNR technology would support BG, and similar patients, in continuing language treatment beyond the limited time spent in a medical/urban setting.

Based on prior research with the stroke population (24–26), we hypothesized that this treatment would be effective for several reasons. First, Integrated Conversation Treatment (ICT), targets language domains (word finding, sentence generation, and conversational interactions) that have been identified as being particularly vulnerable to brain tumor pathology (4, 8, 27). Second, in line with a large body of learning (28) and neurorehabilitation (25, 29–31) research, ICT explicitly trains *generalization* of isolated "part-task" (word/sentence production) to "whole-task" (functional communication) performance. Furthermore, ICT is a problem-based treatment approach that centers on authentic patient-selected communication goals. As such, successful acquisition of targeted treatment goals has the potential to have an immediate and positive impact on quality of life. While this is an important outcome for all patient populations, it is especially important for BT survivors who may be facing significant mental health/motivational issues associated with depression, anxiety, pain management, and/or malignant conditions with high mortality rates. Specific study objectives were to: (1) Present a detailed clinical history and cognitive-communication profile of a long term glioblastoma survivor; (2) Evaluate the efficacy of ICT; and (3) Assess feasibility of TNR by monitoring treatment progress and patient satisfaction during alternating face-to-face (F2F) and TNR treatment blocks.

CASE DESCRIPTION

Medical History

BG, a 35-year-old right-handed monolingual English-speaking Caucasian male initially presented to the ER 6 years prior to this study after experiencing a "fuzzy feeling, mumbling, and aphasia" followed by seizure activity. A malignant (grade IV) $3 \times 2.5 \times 2$ cm irregularly-shaped glioblastoma in the left frontal lobe extending deep to the insula was subsequently identified and excised followed by radiation and chemotherapy (temozolomide) without any subsequent long-term behavioral deficits. Approximately 10 months later, there was a recurrence of the tumor. Subsequent treatment included a second resection with placement of Gliadel wafers (chemotherapy), followed by additional radiation and chemotherapy (azixa trial lasting 18 months). The most recent MRI reports showed no evidence of tumor progression.

Therapy History

Immediately after the second surgery, inpatient reports described BG as having mild right hemiparesis and moderate-severe expressive aphasia. Initial speech therapy targeted naming, left/right discrimination, reading short sentences, and legibly writing his full name, address, and date. Consistent with prior reports of glioma patients (32), BG demonstrated significant gains following surgery and was discharged from physical and occupational therapies after 2 months. However, speech therapy targeting speech motor control, language, processing speed, and verbal memory have been ongoing. Clinical reports indicate that BG has continued to make steady gains throughout this time.

Social and Vocational History

At the time of the initial diagnosis, BG was working full-time as an electrician, pursuing a teaching degree, and living with his wife and two daughters (aged three and five) in a remote rural area. Since that time, BG has continued to live with his family (daughters now aged eight and ten), but has not returned to complete his teaching degree. Except for several months working as a laborer on a farm, he has remained unemployed.

TIMELINE

A single subject (ABABA) multiple baseline design (**Table 1**) was applied to assess potential treatment effects with replication across behaviors. Treatment (8 weeks total) included four consecutive two-week blocks: (1) Treatment I in F2F context; (2) Treatment I in TNR context; (3) Treatment II in F2F context; and (4) Treatment II in TNR context.

THERAPY PROGRAM

Assessment

Initial Screening and Selection of Language Treatment Goals

BG passed a hearing screening and reported no pre-tumor history of language, learning, psychiatric, or neurological impairment. During a structured interview using the Assessment for Living with Aphasia (33), BG communicated that he viewed talking and writing as his most significant communication impairments. He expressed frustration that he was no longer able to work and provide financially for his family. He also indicated that he missed being able to participate in complex conversations with his family and friends. BG said that he felt comfortable talking at home and in the community but was concerned that people did not respect him or view him as competent/intelligent. Following this interview, an assessment and treatment plan were developed based on BG's two self-selected treatment goals: to improve his ability to talk with his daughters about their interests (D) and to talk with friends about sports (S).

Pre- and Post-treatment Testing

Standardized measures (**Supplementary Materials 1**) were selected to evaluate a range of speech, language, and cognitive domains. We hypothesized that potential generalization effects would be evident on measures of communication (motor speech, naming, sentence generation, discourse production, and functional communication) but not on measures of non-verbal/visuo-spatial abilities. Statistically significant change (e.g., cut-off scores, z-scores, & SEM) was determined using published data/procedures (33–45). For the ALA (33) ratings and AphasiaBank discourse analyses (44, 45) experimental data were used to compute descriptive statistics (pre- and post-treatment means, SD, and SEM). A difference of $\geq$2 SEM was interpreted as statistically significant change.

Weekly Probe Testing

The primary outcome measure was production of fluent meaningful speech in the context of functional communication. Standardized coding procedures (45) were used to code/tally Correct Information Units/minute (CIUs/utterance). Weekly probes consisted of four 5-min topic-focused conversations. Each conversation was with a different conversational partner (CP). Two conversations (with CP1 & CP2) focused on sports and two conversations (with CP3 & CP4) focused on his daughters' interests. The participant and CP were told to talk about their respective topics for 5 min. No other information or structure was provided. Mean point-to-point coding reliability across conversations was 91% (range: 82–100%).

Satisfaction Survey

BG completed a 24-item Satisfaction Survey after each treatment block to evaluate treatment delivery in F2F and TNR contexts. The survey, developed specifically for this study, was based on content from other published TNR satisfaction surveys (46–49) and more general aphasia/communication rating scales (33, 43, 50, 51). Items focused on autonomy, communication, treatment, treatment location, and treatment technology/equipment.

Integrated Conversation Therapy

Treatment Protocol

Sessions included three 15-minute activities: Word retrieval training, Topic-comment training, and Conversation practice (**Supplementary Materials 2**). To address impairments associated with motor planning and processing speed, at the start of each activity BG was reminded to speak as clearly as possible. If an utterance was dysfluent and/or unintelligible during any of the tasks he was prompted "to stop, breathe, and think about what he wanted to say."

Sessions began with word retrieval training modeled after semantic feature analysis (52, 53). Words (1–5 syllable nouns) were chosen by the participant in consultation with the clinician. Stimuli included 40 words related to sports and 38 words related to his daughters' interests (**Supplementary Materials 3**). The two sets of words were further divided into two balanced (frequency, length, phonetic complexity) subsets used for F2F and TNR delivery.

Topic-comment training, modeled after Response Elaboration Training (RET) (54, 55) trained word retrieval and fluency (CIUs/utterance) of target words in the context of sentences. The clinician produced ten novel topic-related comments/questions (e.g., I watched the super bowl last night) to elicit a spontaneous comment/question from BG (e.g., What team were you rooting for?).

Conversation practice, also modeled after RET, targeted retrieval of trained words and sentences in the context of topic-focused conversations. BG selected a topic related to either sports (Sports Conversation treatment) or his daughters' interests (Daughters' Interests Conversation Treatment).

Dosage and Setting

Four 45-min sessions per week for 8 weeks were conducted in a quiet setting. F2F sessions occurred in a clinical suite with BG sitting opposite the clinician. For TNR sessions, BG participated from his home and communicated with the clinician (located at the clinic) by computer.

Tele-Neurorehabilitation System Architecture

TNR sessions were run via internet (5 mb/s incoming signal; 1 mb/s outgoing signal) in real time using commercially available CISCO jabber videoconferencing system software. Clinicians used a CISCO SX10 videoconferencing system integrated with a remote-controlled HD (768 × 448) video camera, a CISCO CTS-QS C20 microphone, and a widescreen (30″)

TABLE 1 | Timeline and study design showing assessment schedule in relation to treatment phase.

Study phase	(A) Pre-treatment		(B) Treatment I conversations about Sports				(A) Break	(B) Treatment II conversations about daughters' Interests				(A) Post-treatment	
Timeline (week)	1	2	1	2	3	4	1	1	2	3	4	1	2
Treatment delivery			F2F	F2F	TR	TR		F2F	F2F	TR	TR		
Assessment	Screen												
	Test Battery											Test Battery	
	Probe	Probe	Probe	Probe	Probe	Probe	Probe	Probe	Probe	Probe	Probe	Probe	Probe
				Survey		Survey			Survey		Survey		

F2F, face-to-face delivery; TNR, telerehabilitation delivery; Survey, Satisfaction Survey.

Samsung display. The participant accessed the system from home via Digis broadband internet using a system-configured widescreen (15.6″) Dell Inspiron 1545 (2GHz dual-core, 1MB, 800 MHz processor; 3GB RAM) laptop computer equipped with a Microsoft LifeCam Cinema 720p HD (30 frames/s) webcam and integrated microphone. Sessions were recorded and stored on an established, controlled-access, secure state education/healthcare server.

Treatment Fidelity

Two graduate students supervised by an ASHA certified SLP (study authors) administered the therapy. An anlysis of treatment fidelity (sequential completion of treatment steps as specified in **Supplementary Materials 2**) showed 93% concordance between actual and specified study procedures.

Outcomes

RQ1 Baseline Cognitive-Communicative Profile

Performance (**Supplementary Materials 1**) was above or within the normal range on many measures of apraxia (ABA-2 subtests), comprehension/production of single words and sentences (WAB-R, NAVS), verbal memory (Digit Span), verbal learning (CVLT-2), and non-verbal problem solving (RCPM). Mild impairments were evident on diadochokinetic rate (ABA-2), higher-level naming (BNT), general measures of aphasia (WAB-R), and cognitive-communicative ability (SCCAN). BG's most significant (moderate-severe) impairments were identified on production of words of increasing length (ABA-2), intrusion and false positive errors on delayed recall of word lists (CVLT-2), and discourse production (WAB-R fluency rating & AphasiaBank).

In contrast to relatively preserved production of isolated words and sentences, discourse production was characterized by an atypical fluency pattern, alternating between phases of normal fluent speech, slow effortful groping articulation, and occasional low volume rushes of unintelligible speech. Marked word finding behaviors (false starts, fillers, pauses, phonemic, and semantic paraphasias, circumlocution), paragrammatism (simplified perseverative structural patterns with functor errors), as well as reduced information content were also more pronounced during connected speech than in production of isolated words and sentences.

Using the WAB-R criteria, BG was classified as having a mild (AQ = 89.2) anomic aphasia. BG self-described his language impairment as significantly impacting his participation in daily activities and his overall quality of life.

RQ2 Treatment Efficacy

Acquisition of target behavior

Production of CIUs/utterance (**Figure 1**) increased during treatment with five of the six conversational partners. Computation of a weighted d statistic (56) using the probe data (top four graphs) revealed a small overall treatment effect size ($d = 0.9$) (**Table 2**).

Pre- and post-treatment standardized test battery (Supplementary Materials 1)

Significant change ($\geq$ 2 SEM) was evident on measures of apraxia (ABA-2 Diadochokinetic Rate & Increasing Word Length), verbal memory (Digit Span Forward & CVLT-2 subtests: Free Recall List B, Short-Delay Free Recall, and Long-Delay False Positives), self-ratings of communication (CETI), self-ratings of living with aphasia (ALA Participation Domain, ALA Personal Domain), and discourse production (AphasiaBank Free Speech). In addition, BG showed a change in diagnostic classification on the BNT (pre-treatment = mild impairment; post-treatment = normal) and the Total Intrusions score on the Delayed Recall Test of the CVLT (pre-treatment = impaired; post-treatment = normal).

RQ3 Feasibility of F2F vs. TNR Treatment Delivery

BG attended all sessions

Treatment data (**Figure 1**) suggest a relatively stable learning curve, regardless of whether the intervention was administered in F2F or TNR contexts. Ratings from the Satisfaction Survey ranged from 3 to 5 (maximum possible = 5). Of the 21 items, ten had identical ratings for F2F and TNR conditions, nine had higher ratings for the TNR condition, and two had higher ratings for the F2F condition. Collapsing across the 21 items and both treatment replications (Sports and Daughters' Interests),

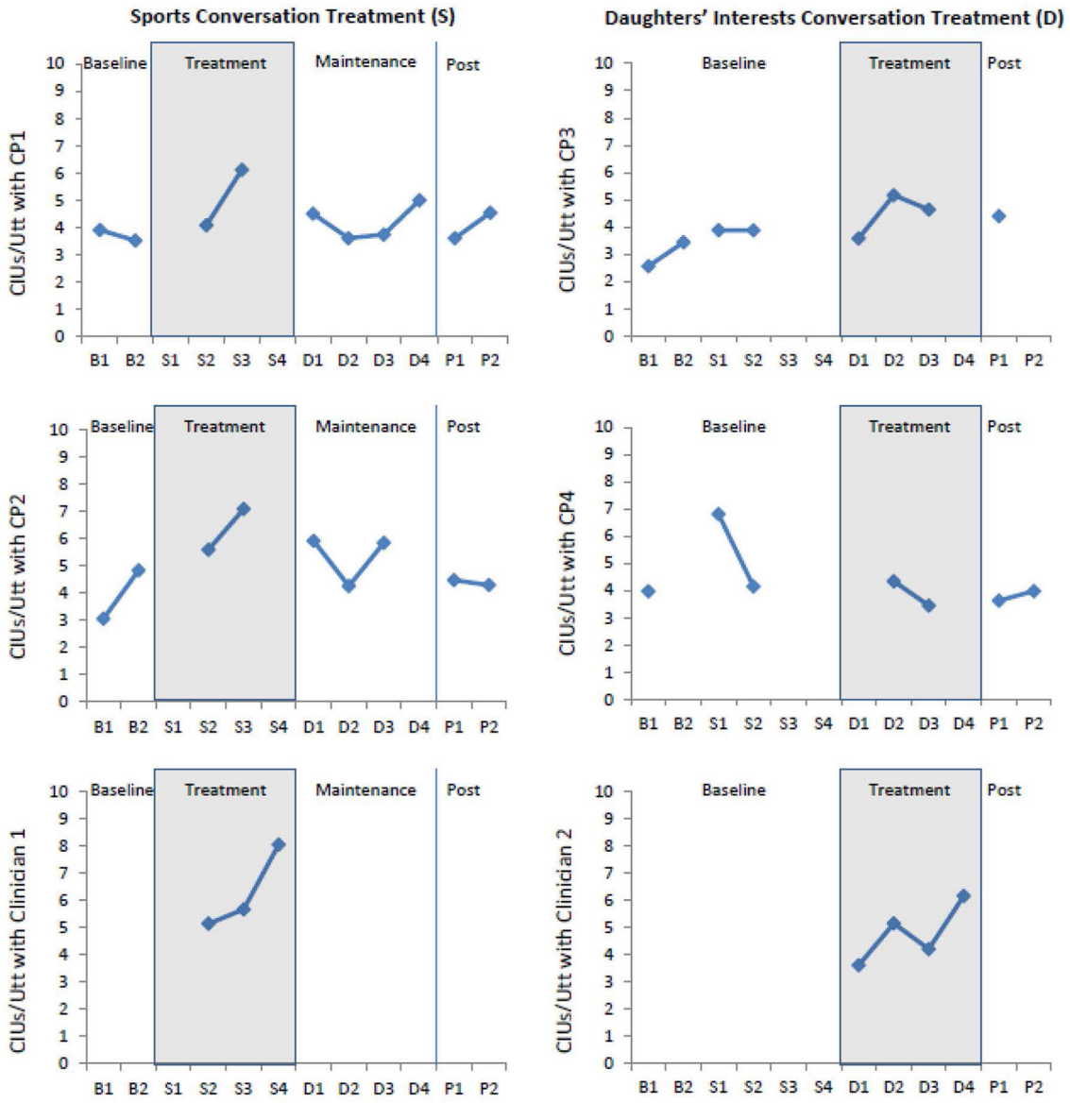

FIGURE 1 | CIU's/utterance produced by BG during probes (top four graphs) and during treatment sessions (bottom two graphs) with six conversation partners (CP1, CP2, Clinician 1, CP3, CP4, and Clinician 2) during Sports and Daughters' Interest conversations throughout baseline, treatment, and post-treatment phases. Missing data from probes (top four graphs) were due to missed appointments by designated conversational partners. To supplement this missing information information, data from conversations with clinicians during treatment session (bottom two graphs) are also included.

TABLE 2 | Treatment effect size with each conversation partner (CP).

	BG sports conversations (with CP1)	BG sports conversations (with CP2)	BG daughters interests' conversations (with CP3)	BG daughters interests' conversations (with CP4)	TOTAL d (sum of weighted d/ sum of observations)
d	1.63	0.8	1.56	−0.7	0.91
Observations	8	7	5	5	25
Weighted d	13.05	5.62	7.79	−3.7	22.8

results of a paired sample t-test revealed a small but statistically significant difference between F2F (mean rating = 4.57, SEM = 0.08) and TNR (mean rating = 4.76, SEM = 0.07) satisfaction ratings ($t = -2.24$, $df = 41$, $p < 0.03$).

DISCUSSION

Cognitive-Communicative Profile

BG performed in the mildly impaired to normal range on many basic measures of cognitive-communicative function. Yet more in depth evaluation revealed moderate-severe impairments affecting motor speech, language, verbal working memory, functional communication, and quality of life. On the WAB-R, BG was classified as having a mild anomic aphasia. However, his communication differed from a classic anomic pattern. The most notable deviations included: fluctuating production (affecting fluency and information content); a marked discrepancy between production of isolated words and sentences vs. spontaneous connected speech; and involvement of more diffuse behavioral signs (specifically motor speech production and verbal working memory). While not characteristic of classic anomia, BG's performance was similar to reports of other BT survivors (27, 57, 58) and to cases of dynamic aphasia associated with BT and/or atypical aphasia resulting from subcortical pathology (59–61). As hypothesized elsewhere (8, 27, 57, 58, 62, 63), these distinct behavioral effects are likely tied to the involvement of widely distributed subcortical networks (associated with speech production, language, working memory, and executive functions) and the unique pathophysiology precipitated by the tumor and/or medical treatments (neurosurgery, chemotherapy, and radiation therapy).

Response to Integrated Conversation Treatment

BG made statistically significant gains on the primary outcome measure (CIUs/Utterance in topic-focused conversations) and on standardized measures of apraxia, discourse production, verbal working memory, functional communication, and quality of life. Responses to the Satisfaction Survey and other anecdotal comments also indicate that BG and his wife perceived the intervention as helpful. For instance, BG described the intervention as being particularly effective relative to prior language therapy and commented that the intervention played an important role in his decision and ability to return to work shortly after this study was completed.

Given that the intervention targeted isolated language production tasks (motor speech control, word finding, sentence generation) *and* generalization of training to authentic everyday conversational interactions, the gains observed across a range of language and communication measures were not surprising. While changes in verbal memory were not anticipated, these findings are consistent with prior research linking language production with verbal working memory (64, 65).

BG's most significant changes were on measures of spontaneous speech, verbal memory, and functional communication; whereas in previous ICT studies (of post-stroke aphasia) greatest gains were seen on standardized measures of naming (BNT) and on a general aphasia battery (WAB-R). Several factors likely contributed to these differences. First, the etiology of BG's aphasia likely contributed to not only differences in baseline performance but also to differences in his responsiveness to treatment. A closely related issue centers on assessment. BG performed at or near ceiling on standardized language measures (WAB-R & BNT) used in previous studies. As recently indicated in the BT survivor literature (57, 66–68), it is likely that these measures (developed for other clinical groups), were not sufficiently sensitive to capture changes in BG's ability level.

It is also likely that modifications of our treatment approach contributed to differences in the observed outcomes and increased carry over to everyday communication. First, to increase personal relevance of ICT, we asked BG to choose not only treatment stimuli (as in previous studies with stroke patients) but also the discourse topic. Personal relevance has been identified as a critical variable in facilitating neuroplasticity (30), positive outcomes in aphasia treatment research (69), and increased language production in cases of dynamic aphasia (60).

A second important modification of our treatment approach was the shift in whole-task training from a picture-based descriptive discourse task (as done in earlier studies) to practiced engagement in authentic conversational interactions. Consistent with previous findings in the aphasia treatment literature (31, 70), we observed substantial variability in performance (and generalization) across discourse genres, topics, and even conversational partners. Notably, the greatest change in performance was observed on the trained conversation task. Results of this study, therefore, add to growing evidence highlighting the multifaceted specificity of discourse processing, and the benefit of directly targeting conversation in therapy (26, 31).

Comparison of Face-To-Face (F2F) and Tele-Neurorehabilitation (TNR) Intervention

BG, showed a relatively stable learning curve (**Figure 1**) acrossF2F and TNR delivery. With respect to the Satisfaction Survey, results indicated a small but statistically significant preference for the TNR condition. In fact, the one negative comment written on the survey was BG's dissatisfaction with the time that it took him to drive to therapy. Collectively these data add to an existing literature supporting the feasibility of TNR and the potential for comparable patient satisfaction with both treatment delivery models (11).

Limitations and Future Research Priorities

These findings reflect data from a single case, therefore more research is needed before inferences can be made to a larger group. Also, we began with F2F treatment (standard delivery model) to ensure that ICT was an effective therapy for BG, before assessing the potential feasibility of TNR delivery. Use of an alternating design (counterbalancing the order of F2F and TNR conditions) and extending the duration of the treatment phase would provide more definitive information about the relative efficacy of F2F vs. TNR delivery. Also, exploring variable dosage levels (e.g., number of sessions/week; adding

"booster" maintenance sessions) would support more flexible clinical applications.

CONCLUSIONS

BG's cognitive-communication profile and response to intervention differed from other individuals who have participated in the ICT protocol. Nonetheless, statistically and clinically significant change were observed on measures of apraxia, spontaneous speech production, verbal working memory, and quality of life. These preliminary findings add to a growing literature suggesting that both conventional and alternate delivery models, such as TNR, may be effective and practical options for brain tumor survivors.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Materials**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Utah State University Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LM and EA conceptualized the study. EA, KT, DA, and LM administered the intervention. LM, EA, CJ, and MJ contributed to the data analyses. LV and DW were responsible for the TNR technology and videoconferencing. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.583452/full#supplementary-material

Supplementary Material 1 | Pre- and Post-testing results on Standardized Tests.

Supplementary Material 2 | Appendix A Treatment Protocol.

Supplementary Material 3 | Appendix B Treatment Stimuli.

Supplementary Material 4 | CARE Checklist.

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Factors Associated With Adherence to Self-Managed Aphasia Therapy Practice on a Computer—A Mixed Methods Study Alongside a Randomized Controlled Trial

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Background: Aphasia is a communication disorder often acquired after a stroke. Independent use of specialist aphasia software on a home computer is a form of asynchronous tele-rehabilitation that can provide increased opportunity for practice of rehabilitation exercises. This study aimed to explore the factors associated with adherence to self-managed aphasia computer therapy practice.

Method: A mixed methods exploration of adherence was conducted alongside the Big CACTUS randomized controlled trial [ISRCTN: 68798818]. The trial evaluated the clinical effectiveness of self-managed aphasia computer therapy. This study reports secondary analysis of data from participants randomized to the computer therapy group to investigate whether any demographic, clinical or intervention variables were associated with adherence to therapy practice. A sub-sample of the same participants took part in qualitative interviews exploring the factors perceived to influence the amount of aphasia computer therapy practice undertaken. Interviews were analyzed thematically. A convergence-coding matrix was used to triangulate the two sets of findings.

Results: Data from 85 participants randomized to the computer therapy group were included in the quantitative analyses. At a clinical level, a greater length of time post-stroke was associated with higher adherence to self-managed aphasia therapy practice on a computer. At an intervention level, length of computer therapy access and therapist time supporting the participant were associated with greater adherence to computer therapy practice. Interviews with 11 patients and 12 informal carers identified a multitude of factors perceived to influence engagement with tele-rehabilitation by people with aphasia. The factors grouped around three themes: capability to use the computer therapy, having the opportunity to practice (external influences and technological issues) and motivation (beliefs, goals and intentions vs. personality, emotions, habit and reinforcement). Triangulation demonstrated convergence for the finding that participants' practiced computer-based therapy exercises more when they received increased support from a speech and language therapist.

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Conclusion: Clinicians delivering asynchronous tele-rehabilitation involving self-management of aphasia therapy practice on a computer should consider the factors found to be associated with engagement when deciding which patients may be suited to this option, as well as how they can be supported to optimize the amount of practice they engage in.

Keywords: aphasia, stroke, adherence, tele-rehabilitation, computer therapy, word finding

INTRODUCTION

Aphasia is a communication disorder affecting speaking, listening, reading, and writing, often acquired after a stroke. Approximately one third of stroke survivors experience aphasia (1). Communication difficulties are known to reduce social participation in all aspects of life including domestic life, employment, and relationships with family and friends (2). Speech and language therapy for people with aphasia (PWA) aims to improve the ability to communicate and participate in everyday activities by directly addressing specific language impairments or by teaching strategies that compensate for the impairment. The most recent Cochrane Review of speech and language therapy for aphasia following stroke found evidence of the effectiveness of speech and language therapy compared to no treatment, but there is no evidence that one treatment was more effective than another (3). However, functional communication was found to benefit from therapy delivered at a high intensity, high dose, or over a long duration (3). There is ongoing debate about whether it is the intensity or total dose of therapy that enables it to be most effective; however, irrespective of favoring massed or distributed practice, there is agreement that more is better (4). It is also known that PWA can continue to recover long after they have had a stroke (5). However, due to resource constraints, limited speech and language therapy is provided beyond the first few months post-stroke in the United Kingdom (UK) (6). One potential solution to address the need to provide more therapy, over a longer period, is to provide greater opportunity for independent practice supported by technology.

Impairment-based speech and language therapy aims to promote neuroplasticity for language (7). Key principles underpinning neuroplasticity include: "use it and improve it," specificity matters (the nature of the therapy dictates the nature of plasticity), salience matters (the training experience must be sufficiently salient to induce plasticity), intensity matters (sufficient training intensity is required to induce plasticity), and repetition matters (sufficient repetition is required to induce plasticity) (7). Deliberate practice facilitates the opportunity for repetition in order to improve skill acquisition (8). Carrying out that practice independently in their own home allows patients to have autonomy to carry out therapy whenever and wherever they chose, as well as increasing accessibility for those in rural and remote locations (9). Adherence to independent practice has been found to be facilitated by individualized therapy approaches, positive reinforcement, goal setting, feedback and problem solving (10, 11). Computerized speech and language therapy is thought to be an efficient solution to provide therapy in the longer term as it provides maximum opportunity for practice beyond that available through face-to-face interaction with a speech and language therapist (SLT) (12). Computerized home-based therapy for aphasia has been delivered through software programs (e.g., AphasiaScripts™) (13), specifically designed apps (e.g., TACTUS Language therapy©) (14), and generic apps (e.g., iBooks) (9). Asynchronous tele-rehabilitation is a service delivery model that enables patients to carry out independent practice of computer-based rehabilitation interventions in their own time, with monitoring and adaption of therapy exercises carried out asynchronously (15). The Big CACTUS trial was the first fully powered, randomized controlled trial to evaluate the clinical and cost-effectiveness of computer speech and language therapy for aphasia in the long-term post stroke (16, 17). In total, 287 participants were randomized to receive either the asynchronous tele-rehabilitation intervention, attention/activity control (puzzle book and phone calls) or usual care. The trial found that the intervention improved word finding, but this did not translate to improved conversation or quality of life. This suggests that the intervention is useful for improving the word-finding impairment. However, it might need adapting or to be used within a broader program of therapy to enable the benefit to translate to improved conversation.

Independent use of specialist aphasia software on a home computer can provide increased opportunity for the practice of rehabilitation exercises. The Big CACTUS trial confirmed that this form of tele-rehabilitation increased the amount of practice carried out over a 6-month period for a relatively low-cost of £733 per person, compared to £1,400 for the same amount of face-to-face therapy (17). Participants using the aphasia computer therapy practiced for a mean of 28 h (SD 25.6) compared with a mean of 3.8 h (SD 7.4) of usual care that was received by all participants over the same 6-month period. The large standard deviation demonstrates that there was significant variation in the amount of independent practice conducted (0–104.5 h), thus demonstrating that providing the opportunity for more therapy and the PWA actually carrying out more therapy do not necessarily equate. When rehabilitation exercises are delivered in their own home as a self-managed intervention, patients can decide to carry out as much or as little as they choose. This exploratory study sought to understand the reasons for variation in adherence to aphasia computer therapy in order to help clinicians target computer aphasia therapy at those who are most suited to this approach and identify how adherence might be optimized.

Carrying out regular independent practice of rehabilitation exercises requires behavior change (11). One of the most influential behavior change frameworks is the COM-B system, which proposes that it is a combination of capability, opportunity and motivation that determines whether or not a behavior will be enacted (18). The three causal elements of the COM-B framework can be further sub-divided. Capability is divided into physical and psychological capability, with physical capability referring to elements such as physical strength and skills, and psychological capability referring to having the psychological resources and skills to comprehend and perform the behavior (18). Opportunity is divided into the opportunity provided by the physical and social environment. The physical environment relates to aspects such as resources or location and social environment relates to aspects such as culture and language. Motivation is divided into reflective and automatic processes. Reflective processes require planning and evaluation, whereas automatic processes are based on basic drives, emotional responses, learnt associations and habit (18). The COM-B system was selected by the authors as a sensitizing framework to help interpret and structure the findings of this exploratory study.

The aim of this study was to explore the factors associated with adherence to self-managed aphasia computer therapy to help identify those individuals for whom this form of tele-rehabilitation may be best suited, and help clinicians optimize conditions to maximize engagement.

MATERIALS AND METHODS

Design

A concurrent triangulation mixed methods approach was adopted to explore the factors associated with adherence to aphasia computer therapy (19). The qualitative exploration of adherence investigated a wide range of factors influencing patient's engagement with this tele-rehabilitation approach. The quantitative analysis was more limited as it could only include variables for which data had been collected within the Big CACTUS trial. Employing a concurrent triangulation approach ensured a greater breadth of possible factors were explored, whilst also capitalizing on the high quality data available from the Big CACTUS trial, and enabling cross-validation of the findings through triangulation of the two data-sets. The authors adopted a subtle realist stance, meaning that we only know reality from our own perspective of it (20), and therefore placed equal value on the qualitative and quantitative findings whilst acknowledging the limitations of both approaches. This study was conducted as part of the first authors PhD (21).

Participants

The Big CACTUS trial recruited participants from National Health Service (NHS) speech and language therapy departments across the UK, aphasia support groups and advertisements displayed in public places. The inclusion criteria were: diagnosis of aphasia caused by a stroke, stroke having occurred 4 months prior to randomization, minimum 18 years of age, score between 5 and 43/48 on the Naming Objects sub-test of the Comprehensive Aphasia Test (CAT) (22), ability to perform a simple matching task in StepByStep with at least 50% accuracy to confirm they could use the software, and the ability to repeat at least 50% of words in a word repetition task. The exclusion criteria included the patient: requiring treatment in a language other than English, already using a computer therapy program to aid word finding, or having another pre-morbid speech and language disorder. A Consent Support Tool (23) was used to identify the support required to enable the patient to provide written informed consent or to identify those patients for whom a carer was required to provide written consent or a declaration of belief that they wished to participate. In addition to the trial inclusion criteria, participants also needed to have been randomized to receive the computer therapy intervention in the Big CACTUS trial and have practice data recorded for >3 months to be included in the secondary data analysis reported here.

A sample of those participants whose data were eligible for inclusion in the secondary data analysis were invited to take part in a qualitative interview. Patients with the most severe aphasia, who were unable to comprehend two key words in a sentence according to the Consent Support Tool (23), were excluded from the qualitative interviews as it was unlikely they could be supported sufficiently to understand the questions asked. However, in order to ensure that the views of patients with more severe aphasia were included we invited their carers to participate in a carer-only phone interview. All participants provided written informed consent.

Maximum variation sampling was used to identify a heterogeneous sample comprising participants who had carried out the highest and lowest amounts of practice in order to maximize the diversity of experience within the sample, as well as enabling the identification of important shared themes that cut across cases (24). Eligible Big CACTUS trial participants were listed according to the amount of practice carried out over the 6-month intervention period. Working inwards, those at the top and bottom of the list were invited to participate first to increase the heterogeneity of the sample. Sample size was determined by the concept of data saturation, which states that data collection stops when no new themes emerge from the data (25).

Intervention

The tele-rehabilitation intervention, referred to as the StepByStep computer therapy approach for the NHS, comprises the specialist StepByStep© aphasia software, with therapy set-up including personalization of vocabulary and tailoring of the exercises according to the individual's impairment provided by a SLT. In addition, on-going support is provided by a volunteer or therapy assistant to enable the PWA to carry out independent practice (16, 17). PWA were recommended to carry out 20–30 min of therapy per day over a 6-month period. This information was conveyed by the SLT and/or volunteer during a face-to-face demonstration of how to use the therapy. An information leaflet about the therapy was provided as a reminder. All support from SLTs or volunteers/assistants was provided via face-to-face contact, email, or telephone. The therapists were required to set up the computer therapy with tailored exercises and personally relevant practice items and provide a demonstration of how to use the therapy, but the number of contacts was not specified.

Volunteers or therapy assistants were asked to provide 1 h of support per month. Support was recorded for 90% of participants (86/96) and one participant declined to receive the support offered. A median of 4 h 15 min of support was provided. As a pragmatic trial, there was no minimum amount of practice or number of sessions. Big CACTUS used available NHS resources and SLTs working in clinical practice to deliver the intervention (17). Additional detail about the delivery of the intervention within the Big CACTUS trial is available in the main results paper (16) and final report: https://www.ncbi.nlm.nih.gov/books/NBK556708/ (17).

Quantitative Data Collection

All quantitative data informing the secondary data analysis were collected as part of the Big CACTUS trial (ISRCTN: 68798818). Data were collected by SLTs who visited the participants at their home to conduct language assessments and collect other necessary information. SLTs also documented the activities and amount of time they and the volunteer/therapy assistant spent supporting the participants, in order to be able to describe how the intervention was actually delivered (17).

The total amount, or dose, of computer therapy practice completed by the PWA was selected as the dependent variable for the purpose of this analysis as it is the measure of adherence most frequently described in the aphasia literature (26). Total practice time (hours) completed by participants was recorded on an electronic file (called a key file) by the StepByStep computer therapy program. The independent variables were divided into demographic, clinical, and intervention variables.

Demographic variables included: gender (male or female); age ($\leq$55, 56–65, 66–75, $\geq$76 years old); presence of an informal carer (yes or no; an informal carer referred to a friend or family member); whether or not they had attended a support group in the 3 months prior to entering the trial; whether or not participants had internet access in their home and which site they were based at (recruiting Speech and Language Therapy department).

Clinical variables included: time post-stroke (years); number of strokes; type of aphasia (anomic, non-fluent, mixed non-fluent or fluent determined by therapists clinical judgement); evidence of apraxia of speech (yes/no based on therapists clinical judgement); severity of word-finding impairment (assessed by Naming Objects sub-test of the CAT) (22); comprehension ability (assessed by Comprehension of Spoken Sentences sub-test of the CAT); participants' own perception of communication related social participation and quality of life (assessed by Communication Outcome after Stroke (COAST) score) (27); and whether or not they had received care for communication difficulties in the 3 months prior to entering the trial.

Intervention variables included: the type of device used (tablet, laptop or desktop computer); who the device was owned by (owned by participant or loaned to participant); and how long the participant had access to the computer therapy software (number of days calculated based on date of provision, removal, and periods of inaccessibility recorded by the SLT) and therefore the opportunity to practice. Activity logs completed by the therapists recorded: (1) therapist time supporting the participant (minutes; this included providing technical support and monitoring the participants progress, directly or indirectly, and making adaptations to the therapy exercises; initial tailoring time not included); (2) therapy assistant/volunteer time supporting the participant (minutes; this included time spent setting-up/adjusting the computer or microphone, encouraging/motivating use of the computer therapy, providing assistance with using the software, and conversations to practice using the words they were learning with the software in context); and (3) therapist time spent with the therapy assistant/volunteer (minutes; including providing training, supporting the assistant/volunteer, providing technical support or monitoring a feedback form).

Demographic and clinical variables were collected prior to the participant's randomization in the Big CACTUS trial, whereas intervention variables were time-dependent co-variates having been collected after the participant had been randomized to the trial and at the same time as the adherence data was being collected. As such, temporality (cause proceeding effect), one of the Bradford-Hill criteria (28) for determining causation, cannot be assumed for the intervention variables, which is why the study can only report associations.

Qualitative Data Collection

Participants were approached via an invitation letter and information sheet, in an accessible format for patient participants, followed by a telephone call from the first author. Interviews with patients took place face-to-face to enable the use of communication strategies. Carer-only interviews took place over the telephone. If both the patient and carer agreed to participate, the author sought to interview them separately, where possible, to allow the PWA to share their views without interruption. Informal carers who did not participate in the Big CACTUS study were asked to complete a short form collecting basic demographic information already collected about the informal carers participating in the Big CACTUS study (e.g., sex, date of birth, and relationship to PWA). The interviews were recorded using a digital recorder and transcribed verbatim. Transcriptions were checked for accuracy.

The development of the interview schedule was influenced by the COM-B system of behavior change (18). All interviews followed the same broad structure (see **Table 1**); however, the interview schedule for patient participants was tailored to their communication ability and supported with visual aids where necessary. The interview schedule was broken down into smaller more manageable questions categorized according to how grammatically and conceptually complex the question was: (1) all PWA were asked the most simple questions supported by visual prompts or cues (i.e., calendar) or a picture selection task to support participants to respond, (2) more complex questions/prompts were asked only of those PWA who were able to answer the first level questions with ease, and (3) the most complex questions were only asked of those PWA who answered the second level questions with ease. A picture selection task was only offered if a verbal response was not provided. The picture cards were developed on the basis of the findings from an earlier study exploring the acceptability of a similar intervention

TABLE 1 | Summary of questions from the interview schedule.

Interview schedule
Can you tell me about how your communication problem affects your life?
How important is it to you that your communication problem improves?
Can you tell me about the speech therapy you have had before?
When [therapist name] told you about the computer therapy, what were your first thoughts?
When did you start using the computer therapy? When did you finish?
How many times a week did you practice? What made you practice more? What made you practice less?
How long did each practice session last? What made you practice for longer? What made you practice for less time?
How often and for how long did [therapist name] and [volunteer name] suggest you should practice?
Can you tell me about using the computer therapy?
How often did you see [volunteer name] and how long for? Can you tell me about your relationship with [volunteer name]? What did you do during the visits?
How often did you see [therapist name] and how long for? Can you tell me about your relationship with [therapist name]? How did [therapist name and volunteer name] feel about the computer therapy?
Did anyone else help you with the computer therapy? What help did they provide?

(29) and recommendations from the Big CACTUS Patient and Carer Advisory Group. Each card showed a key concept for the participant to select whether or not it reflected their perspective (see **Figure 1**). The first interview served as an internal pilot after which the author reflected on how the questions were asked and the answers that were forthcoming and made small changes to the wording of the questions as necessary.

When a carer also participated, more conceptually challenging questions were addressed to them if the patient was not able to answer them. Carer-only interviews utilized an interview schedule covering the same concepts, but asking the questions from the perspective of the patient (e.g., how important is it to your husband that his communication problem improves?).

Data Analysis

Exploratory data analysis techniques were employed to investigate the relationships between the independent variables described above and adherence to practice. Analysis was carried out using SPSS v25. The first step was to establish which of the demographic, clinical, and intervention variables (i.e., independent variables) were associated with the dependent variable (total practice time). In order to achieve this, bivariate analyses were conducted using a correlation matrix for continuous variables, independent samples *t*-tests for binary categorical variables, and one-way ANOVA for categorical variables with two or more categories. All independent variables found to be significantly associated ($p < 0.05$) with total practice time were included in a multiple linear regression model. The model was adjusted for age and gender. The original model violated the assumption for homogeneity of the variance. Consequently, a sensitivity analysis was carried out using the square root of total practice time (the dependent variable), which significantly reduced the heteroscedasticity. The sensitivity analysis allowed the original model to be retained. Results of the original model and sensitivity analysis are reported.

Qualitative data were analyzed using thematic analysis, to identify from the patient and carer perspective the factors associated with adherence to aphasia computer therapy (30). The initial step of familiarization was achieved through repeated reading of all transcripts. In-depth paper and pen based coding of a transcript from one high and one low adhering participant resulted in the development of an initial coding framework. The initial coding framework was entered into NVivo 11 (31). During the process of coding subsequent transcripts in NVivo, more codes were added and others were merged, grouped or renamed. Once all transcripts had been coded by the first author (MH), the themes were reviewed by all authors and an external qualitative expert (SA). During the review process it was decided that the sensitizing frameworks underpinning the development of the interview schedule, would be drawn upon to support the data interpretation phase. Therefore, a two-step inductive and deductive analysis process was used in which an initial thematic analysis was mapped onto an established model (32). No tensions arose during the mapping process as the data had a good fit with the COM-B system. The lower level codes (sub-themes) were mainly unchanged; however, some were divided or combined where necessary to map onto the COM-B system. Higher-order theme names were re-defined and the findings were written up (30). In order to explore the similarities and differences between high and low adhering participants, a feature of the NVivo software was used to categorize the transcripts as cases with different attributes (e.g., high vs. low adhering participant) to enable patterns of response to be explored.

The triangulation approach combined the "following a thread" method, whereby each finding from one dataset is followed across to the other dataset (33), and applying a "convergence coding matrix," in which the findings from each study are displayed together along with consideration of the extent to which the findings converge (34). Firstly, the factors associated with adherence identified in the qualitative interviews acted as the thread, which was followed across and searched for in the quantitative findings. The qualitative data continued to be grouped according to the COM-B system (18), thus enabling the quantitative data to be considered in light of this behavior change model. The convergence coding matrix was used to integrate the threads and convergence was coded using the following criteria: "Convergence: where findings directly agree; Complementary: findings offer complementary information on the same issue; Dissonance: findings appear to contradict one another; Silence: themes arising from one component study but not others" (34). Only quantitative variables found to be associated with adherence to aphasia computer therapy practice in the multivariate analysis were included in the triangulation.

Ethical Approval

Ethical approval for the secondary analysis was obtained from Leeds West Research Ethics Committee (REC; 13/YH/0377) and the Scottish A REC (14/SS/0023). Separate approval for the

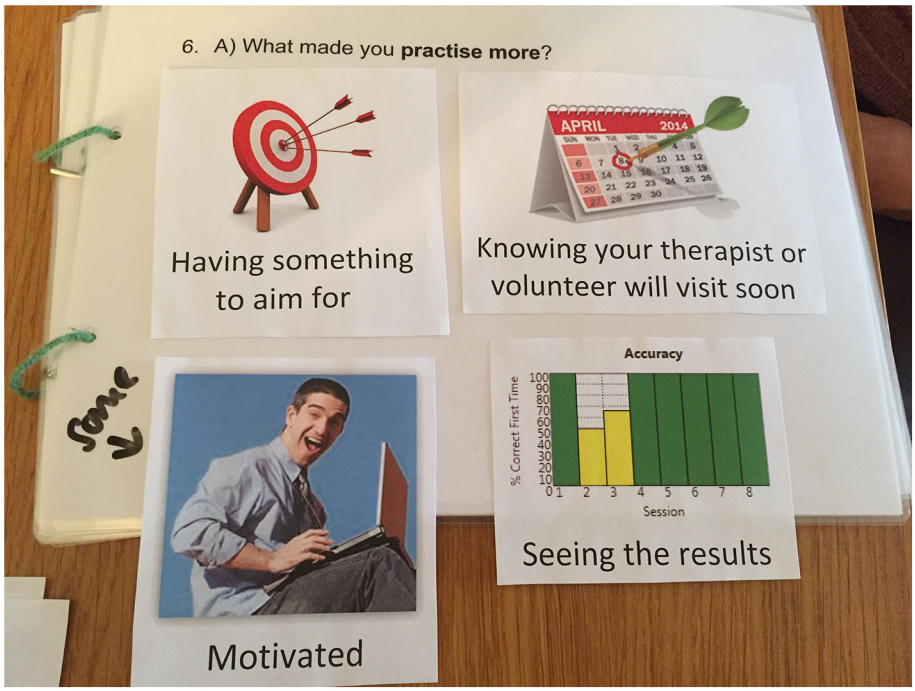

FIGURE 1 | Example of picture selection cards used to facilitate response from participants with more severe communication impairment.

qualitative interviews was obtained from the School of Health and Related Research REC at the University of Sheffield (008063).

RESULTS

Participants in Secondary Data Analysis

The analysis included 85 of the 97 participants randomized to the intervention arm of the Big CACTUS study. Participants with no practice time data ($n = 9$) or partial practice time data (3 or more months data not recorded; $n = 3$) were excluded. The sample included 54% males ($n = 46$). Descriptive data for key variables are summarized in **Table 2**. Findings from bivariate analysis.

The results of the bivariate analysis are presented by variable group.

Demographic Variables

Male participants practiced more ($M = 50.70$ h, SD = 50.97 h) than female participants ($M = 32.51$ h, SD = 30.19 h) and an independent samples t-test determined the difference was statistically significant [$t_{(74.78)} = 2.035$, $p = 0.045$]. Age was grouped into four categories with a similar number of participants in each age group (≤55 $n = 20$; 56–65 $n = 19$; 66–75 $n = 24$; ≥76 $n = 22$). Those aged 56–65 practiced most ($M = 60.43$ h, SD = 42.71 h) and those aged 76 and over practiced least ($M = 30.16$ h, SD = 40.86 h). However, a one-way ANOVA demonstrated that there were no statistically significant differences between age group means [$F_{(3, 81)} = 1.956$, $p = 0.127$]. None of the other demographic variables were found to be significantly associated with total practice time. There was a trend for those with an informal carer to practice more ($M = 46.17$ h, SD = 46.39 h) than those without ($M = 29.08$ h, SD = 28.21 h), but an independent samples t-test established that this was not a statistically significant difference [$t_{(83)} = -1.523$, $p = 0.131$]. There was also no significant difference in the amount of practice carried out by those who attended support groups ($M = 48.80$ h, SD = 52.41 h) compared to those who did not ($M = 36.34$ h, SD = 32.46 h) determined by an independent t-test [$t_{(65.87)} = -1.306$, $p = 0.196$]. There was a slight trend toward those with internet access practicing more ($M = 47.28$ h, SD = 35.06 h) than those without internet access ($M = 36.53$ h, SD

TABLE 2 | Descriptive summary table of key variables.

Variable	Mean	Standard deviation
Total practice time (hours)	30.92	25.36
Age (years)	66.28	12.9
Time post-stroke (years)	2.43	3.03
Length of computer therapy access (days)	139.96	34.64
Therapy assistant/volunteer time supporting participant (minutes)	254.76	107.45
Therapist time supporting participant (minutes)	84.29	92.44
Severity of word-finding difficulties (CAT Naming Objects; maximum score = 48)	25.88	11.53

= 51.49 h); however, the results were not statistically significant as determined by an independent samples *t*-test [$t_{(83)} = -1.14$, $p = 0.258$]. A one-way ANOVA established that there was also no statistically significant difference in practice time between the different sites [$F_{(20, 64)} = 0.872$, $p = 0.621$].

Clinical Variables

There was a weak positive correlation between total computer therapy practice time and number of years post-stroke ($r = 0.23$, $n = 85$, $p = 0.04$). This was the only clinical variable found to have a statistically significant association and therefore the only clinical variable to go forward to the regression model. A bivariate correlation matrix established that all other continuously measured clinical variables had weak, negative non-statistically significant associations with total practice time: number of strokes ($r = -0.18$, $n = 85$, $p = 0.099$), severity of word-finding difficulty shown by CAT naming objects score ($r = -0.052$, $n = 85$. $p = 0.634$), comprehension of spoken sentences ($r = -0.015$. $n = 85$, $p = 0.889$), and PWA rated perception of communication rated using the COAST ($r = -0.010$, $n = 82$, $p = 0.929$). There was a trend toward those who had not received care in the last 3 months practicing more ($M = 47.58$ h, SD = 49.29 h) than those who had received care ($M = 36.46$ h, SD = 35.44 h); however, an independent samples *t*-test established this was not a statistically significant difference [$t_{(83)} = 1.181$, $p = 0.241$]. There was no statistically significant difference in total practice time between those with apraxia of speech ($M = 40.67$ h, SD = 37.90 h) and those without ($M = 43.36$ h, SD = 46.79 h) as shown by an independent samples *t*-test [$t_{(83)} = 0.275$, $p = 0.784$]. A one-way ANOVA found no statistically significant difference in practice time between participants with different types of aphasia [$F_{(3, 81)} = 0.277$, $p = 0.842$].

Intervention Variables

Total practice time was found to be positively correlated with length of computer therapy access ($r = 0.433$, $N = 85$, $p = 0.00$), therapist time spent supporting participants ($r = 0.242$, $N = 85$, $p = 0.026$) and therapy assistant/volunteer session time spent supporting participants ($r = 0.237$, $N = 79$, $p = 0.035$). The amount of time the therapist spent with the therapy assistant or volunteer showed no linear relationship with the total amount of practice and was not statistically significant ($r = 0.069$, $n = 80$, $p = 0.545$). There was a trend toward more practice being carried out by those participants who were practicing on their own device ($M = 50.44$ h, SD = 34.76 h) rather than a device loaned to them ($M = 38.79$ h, SD = 46.58 h); however, an independent samples *t*-test demonstrated that the difference was not statistically significant [$t_{(83)} = 1.141$, $p = 0.257$]. Participants could practice on three types of device: the majority used a laptop ($N = 70$, $M = 41.09$ h, SD = 39.70 h), some used a tablet ($N = 12$, $M = 52.83$ h, SD = 65.05 h), and a small number used a desktop computer ($N = 3$, $M = 29.76$ h, SD = 25.42 h). Whilst there was a trend for participants using the most portable device (tablet) to practice most and the least portable device (desktop computer) to practice least, the number of participants in the three groups was unequal and a one-way ANOVA showed that the difference between the groups was not statistically significant [$F_{(2, 82)} = 0.498$, $p = 0.609$].

Findings From Multivariate Analysis

Multivariate linear regression was carried out to investigate the relationship between practice time (hours) and time post-stroke (years), length of computer therapy access (days), therapist time supporting participant (minutes), and therapy assistant/volunteer time supporting participant (minutes). The model included data from 79 of the 85 participants due to missing data. The analysis was controlled for age and gender. There was a statistically significant relationship between practice time and length of time post-stroke ($p = 0.038$), computer therapy access ($p = 0.003$), and therapist time supporting participant ($p = 0.043$). For each additional year post-stroke, there was a 3.018 h (3 h 1 min) increase in practice time (see **Table 3**). For each additional day of computer therapy access, there was a 0.124 h (7 min) increase in practice time. Furthermore, for each additional minute the therapist spent providing support (including technical support and monitoring/adapting exercises) to the participant the total practice time increased by 0.098 h (6 min). Gender, previously found to be associated with practice time in the bivariate analysis, no longer demonstrated a statistically significant association with practice time in the multivariate analysis ($p = 0.110$). The relationship between practice time and therapy assistant/volunteer time supporting the participant ($p = 0.233$) was also not statistically significant.

Therapy assistant/volunteer time supporting the participant would have been removed from the model due to non-significance; however, it was retained because it was identified to be significant in the sensitivity analysis. A scatterplot of standardized predicted values vs. standardized residuals indicated that the data did not meet the assumption of homoscedasticity. The sensitivity analysis, using a square root model, allowed for the assumption of homoscedasticity to be met, thus confirming the findings of the original model. One notable difference between the two models was that therapy assistant/volunteer time supporting the participants, which was not significantly associated with practice time in the original regression model, was found to be statistically significant in the square root model (see **Table 3**). This will be taken into consideration in the interpretation of results in the discussion.

The R^2 value for the original model was 0.29, so 29% of the variation in practice time can be explained by the model containing age, gender, time post-stroke, length of computer therapy access, therapist time supporting the participant and therapy assistant/volunteer time supporting the participant.

Participants in Qualitative Interviews

In total, 14 interviews were conducted with 23 participants, including 11 PWA and 12 informal carers. The mean interview length was 68 min (ranging from 24 to 103 min). The mean time between the end of the 6-month intervention period and participation in the interview was 247 days (SD = 113.21).

TABLE 3 | Regression coefficients and *p*-values for the original and square root multiple linear regression models.

Variable	Original model			Square root model		
	Coefficient	*p*-value	Confidence interval	Coefficient	*p*-value	Confidence interval
Time post-stroke (years)	3.018*	0.038	0.170–5.866	0.241*	0.028	0.027–0.455
Length of computer therapy access (days)	0.124*	0.003	0.043–0.204	0.007*	0.029	0.001–0.013
Therapy assistant/ volunteer time supporting participant (minutes)	0.054	0.233	−0.036 to 0.144	0.007*	0.041	0–0.014
Therapist time supporting participant (minutes)	0.098*	0.043	0.003–0.193	0.009*	0.020	0.001–0.016
Gender	−14.453	0.110	−32.233 to 3.327	−0.635	0.347	−1.971 to 0.701
Age (years)	2.400	0.556	−5.686 to 10.485	−0.071	0.818	−0.678 to 0.537

**Significant at 5% level.*

Nine interviews included the PWA and carer, three were carer-only interviews and two were PWA-only interviews. All carer-only interviews were conducted with the carers of low adhering patients. Of the PWA participating, or described in a carer-only interview, the mean age was 65 years old (ranging from 48 to 85) and 10/14 were male. The mean practice time for high adhering (HA) participants was 67 h 21 min, and for low adhering (LA) participants, 13 h 13 min.

Both the low and high adhering groups included participants whose aphasia was classified as mild (score 65–90%), moderate (score 35–64%) and severe (score 10–34%) on the CAT naming objects assessment (22). With the exception of one participant who died prior to the 6-month outcome assessment and one participant who did not carry out any independent practice, all participants showed some improvement on the personal vocabulary naming test, in which they had to name the items they were practicing on the StepByStep software. The mean age of the carers was 61 years old (ranging from 46 to 76) and one was male. The relationship of the carers to the PWA included: eight wives, one partner, one mother, one daughter and one son.

Findings From Qualitative Interview

The factors grouped around three themes influenced by the COM-B system (18): capability to use the computer therapy, having the opportunity to practice, and motivation. The findings are summarized in **Table 4**.

Capability to Use the Computer Therapy

Psychological capability was discussed in relation to participants' knowledge of the intervention, understanding of their own condition and the impact their cognitive impairment had on the amount of practice conducted. Participants' recall of the recommended amount of practice they were expected to carry out was variable. Most participants recalled the recommended duration specified in the treatment manual (20–30 min), but the recommended frequency of practice recalled by participants varied from "*everyday*" to a "*few times a week*" with no clustering of responses around the recommendation that practice should be carried out every day as specified in the treatment manual. Some participants described relatively strict practice guidelines from therapists; however, low adherers more often felt the decision regarding whether or not to practice was based on personal preferences.

> *R15/01 carer: She said obviously don't let it take over your life but she really sort of left it to us to work out fitting into the lifestyle as to how much he should or shouldn't do. (LA)*

Aphasia is a complex condition and participants had varying levels of understanding or knowledge about their own condition. The lowest adhering participant, who scored <50% on the naming assessment at baseline and 6 months, reported that he could name all of the vocabulary available to practice on the computer, therefore demonstrating a lack of awareness, or possibly denial, of their own communication impairment, which might explain their lack of motivation to practice. Some other low adhering participants expressed similar thoughts. In contrast, having more knowledge and understanding of aphasia, as well as having more insight into the impact their communication impairment had on their lives was a motivating factor for those participants who were able to describe how their impairment affected their everyday life.

> *R16/07: Yeah. It wasn't making any good to me anyway, cause I knew exactly what they were cause they're already in there. I could say all of these things. (LA)*

> *R10/02: I realise my language was letting me down see. (HA)*

Some perceived practice to have been limited by stroke-related cognitive impairments, such as difficulties with memory, concentration, and fatigue, and described strategies they had identified to overcome the impact of cognitive impairment, such as practicing at a time when they are most alert or moving to a quieter area of the house.

> *R13/21 carer: She can't concentrate on more than one thing at once, if you know what I mean and children sometimes can be, you know, in the background and not even being noisy, but you are conscious of them, aren't you? (LA)*

TABLE 4 | Factors associated with adherence to aphasia computer therapy categorized into themes using the COM-B system.

Capability	Opportunity	Motivation
Physical • ↕ Ability to use computer therapy software • ↑ Assistants/volunteers help PWA to develop the skills required to use the computer therapy	Physical • Computer therapy software problems (↓issues with voice recognition; ↓stability of the software; ↑stability of the software was improved via software updates) • ↓Computer hardware problems • Features of the software that facilitated more practice (↑ personalization of vocabulary; ↑therapy in home environment; ↑ independence HA only) • Barriers to practice (↓periods of illness; ↓other commitments; ↓engaging in alternative therapeutic activities) • Availability of support (↑more input from supporters; ↑informal carers of participants who could not use computer therapy independently)	Reflective • Beliefs about capability (↓capability concerns often based on lack of prior computer experience; ↑high self-efficacy HA only) • Beliefs about consequences (↑expectation of anticipated outcome influenced by supporters; ↓pessimism) • Goals (↑distal goal associated with regular practice; ↑proximal goal associated with longer practice session; ↓mismatch between personal goal and intended outcome of computer therapy) • Stability of intentions (↓ LA described decline over time) • ↓carer more motivated than PWA
Psychological • ↕ Knowledge of recommended practice time • ↕Understanding/knowledge of own condition • Cognitive impairment and fatigue (↓forgetting; ↓concentration problems; ↓fatigue; ↑strategies to overcome e.g., practice certain times of day)	Social • ↑ External support (importance of input from SLT or volunteer/assistant) • ↑ Social pressure (caused by impending visit from supporter)	Automatic • Emotion (↓low mood or negative attitude on given day) • Personality (↑determined/perfectionist) • Habit (↑routine pattern of practice) • Reinforcement (↑feedback about practice time; ↕feedback about performance)

↓, factor associated with less practice; ↑, factor associated with more practice; ↕, factor associated with both more and less practice.

Another carer described how impaired cognitive functioning prevented independent practice meaning someone had to be available to help him to use the computer therapy, thus demonstrating an association between reduced capability and reduced opportunity for practice.

> *R01/40 carer: He couldn't quite work everything out on his own so it was always with somebody. (LA)*

Low-adhering participants with less computer experience also described challenges related to their ability to physically navigate the computer therapy. Participants felt the assistants/volunteers played a vital role in overcoming this barrier.

> *R13/21 carer: I think just sorting out the programme, you know, how to get from one bit to the other and sometimes, you know, it was a bit difficult but I think when [assistant] came she sort of, you know, showed her how to get from one bit to the other. (LA)*

Having the Opportunity to Practice

The physical aspects of opportunity predominantly related to the StepByStep software and the hardware to run it on, as well as the support provided by SLTs/volunteers/therapy assistants. Computer therapy software problems were described as a significant barrier to practice. In particular, problems were encountered with the voice recognition component of the software, which provided feedback on the participant's performance. Whilst nearly all of the participants described the issues with voice recognition as frustrating, some participants continued to practice with work arounds suggested by therapists, including being told to skip that aspect of the computer therapy or in some cases the therapist turned off the voice recognition component. However, for some participants, particularly those who perceived a need for reinforcement, skipping the voice recognition step was not a satisfactory solution and resulted in reduced practice. The other issues with the software reported by participants related to the stability of the software including the software crashing and not being able to move between the different sections or exercises within the software. Some of the issues with the stability of the software related to the fact that the software was an early release of version 5 of the StepByStep software. Several updates were available during the time participants were using the software, and participants described performance improving after updates.

> *R10/02 carer: It was taking a while for the voice recognition on the microphone to log with the computer, you know, and the computer go 'ping', tick, you know. Um, so [PWA] would, would have to say it two, three, four times and that was then stopping the computer and that, that became quite, er, frustrating for him and then sometimes it, it would be just seize up. (HA)*

> *R10/37 carer: I don't think it was perfect to start with. I think it's got better and we've had a couple of updates on it since. (HA)*

A smaller number of participants had computer hardware problems which prevented access to the software. Most of the problems described were the result of using outdated (e.g., slow operating system or operating system not compatible with software) or unfamiliar (e.g., participant having to learn to navigate a new computer system) hardware. The process of determining whether the cause of the problems lay with the technology itself or the way in which the participant was using it demonstrated links between having the opportunity to use

the computer therapy and the participants' actual or perceived capability to do so.

Interviewer: So my next question was what made her practice less?

R03/39 carer: I think cause of the problems with the laptop. (LA)

R03/39 carer: So I never knew whether that was my fault-, whether it was our fault or the computers fault. I mean, I know she did swap it over at one time and I said, 'can you not get us a new one?' 'No we're not allowed new ones', she said, 'it's all old ones'. (LA)

Participants described several features of the software that enabled more practice, including: the ability to personalize the vocabulary, being able to carry out the therapy in their home environment and for high adhering participants the opportunity to engage in independent activity.

R15/37 carer: That was something that made you practice more because they were your words and not just on a computer they were the words you wanted to say. (HA)

R10/37: Oh yes. I get on with it, away-, leave me on my own. (HA)

Barriers to practice identified by participants included: periods of illness, having other commitments (holidays, other appointments, receiving physical care or caring for others) and engaging in alternative therapeutic activities (word games, naming picture cards or educational computer programs designed for children). Carers of low adhering participants described encouraging the participant to engage in these alternative activities when the PWA did not want to use a computer.

R11/03: The only time days off was cause I was going on a cruise. (HA)

R19/19 carer: We done a few little things ourselves off the internet, like we'd have stuff like, for want of a better word, like food and transport and animals and what-have-you. So if she didn't want to go on the computer, which we always tried to get her on the computer at least a half hour every day, we bring out like our own little flip sheets. (LA)

Almost all participants, including those with limited expressive communication (using the picture selection task), expressed that having help and support available from a therapy assistant/volunteer enabled more practice. Some participants, particularly those with more significant communication impairment expressed a need for more help and support. One carer participant reported that their spouse received minimal input from a volunteer/assistant and felt that they would have been more motivated to practice if regular support had been available.

R15/01 carer: It would probably have kept his motivation a little higher in the respect that people would come round, not just to sort of click a memory stick in and take out a reading and see what's been done. I think if someone had come and sat with him, you know, maybe every six weeks, or a month or something like that, you know, somebody who's a professional, not me. (LA)

As well as having the physical opportunity to carry out aphasia computer therapy practice, participants also described the social opportunity afforded by their interactions with others. Several carer participants described the importance of having external support from a speech and language therapist, assistant/volunteer or more removed family member. It was perceived, particularly by the primary informal carers, that support from an external agent was more beneficial and allowed the PWA to engage more fully.

R16/04 carer: Yeah the prompting and the people that aren't me telling him because he doesn't listen to me in the same way and I understand, why would he? But he is better if it is people outside, it would have been better. (HA)

The added benefit of an external supporter was that their visits created a social pressure to carry out more practice. Participants described upcoming visits triggering a sense of obligation to practice and the desire to please the supporter.

R10/37: Erm. We did it because we'd been asked to do it. (HA)

Motivation: Beliefs, Goals, and Intentions vs. Personality, Emotions, Habit, and Reinforcement

In addition to participant's actual capability to engage with asynchronous tele-rehabilitation, they also described beliefs about their own capability to perform the therapy (i.e., self-efficacy). Capability concerns were primarily expressed by low adhering participants based on their lack of prior computer experience. Contrastingly, some high adhering participants described a strong belief in their own ability to engage in computer therapy prior to commencing therapy irrespective of their familiarity with computers, suggesting their beliefs might actually be better predictors of engagement than prior computer experience.

R16/07: Well when they said that I could use a computer I thought, 'I won't be able to do that, how am I going to do that?' [. . .] I mean-, we've never had a computer. (LA)

R11/03: An' I thought I'm not too much into computers, but it's easy innit? Honestly it's easy, just click it and job done. So I thought perhaps I can handle that for half an hour, I can handle that. (HA)

As well as belief in their own capability, participants also described their beliefs about the consequences of the intervention. Participant's descriptions of carrying out continued regular practice responded to an underlying expectation that regular practice would result in an improvement in their performance and overall recovery from their aphasia. The expectation of improvement may have resulted from the fact that most participants perceived that the supporters believed in the effectiveness of the aphasia computer therapy and thought it would be a good opportunity for the PWA.

R06/01: I got the impression she [therapist] believed in it, I think, yeah. Cause if I hadn't got that impression I wouldn't have continued with it, so yeah, yeah. (HA)

Contrastingly, a carer of one of the low adhering PWA described the participant's pessimism and lack of belief that the intervention could produce a beneficial outcome.

R16/07 carer: I think you didn't give it a chance, but you just said, 'what's this doing to help me?' (LA)

High adhering participants and their carers, who typically had a good understanding of their impairment more frequently described their distal goals (i.e., long-term) in terms of what they hoped to achieve from carrying out regular practice. Proximal goals (i.e., short-term) were perceived to motivate longer individual practice sessions. Some participants described goals having been set for them by SLT or assistants/volunteers which they also found to be motivating, particularly when they were combined with feedback from the computer therapy software.

R11/03: She [the assistant] would go through a few of them and see how I was doing and at one stage [therapist] said to her if I want to move on I've gotta get above 90%. And I was getting almost 90% for most of them and that's sort of inspired me to crack on with it. (HA)

For one low adhering participant there appeared to be a mismatch between the goal of the patient and carer (improved conversation) and the perceived goal of the intervention (naming more words).

R16/07 carer: He could say donkey, horse and things like that and name them. But to me that is not what-, he needed conversation, not particular things you need. (LA)

Participants, particularly carers of low adhering patients, described changes in the stability of their intention to practice. Where a change in motivational readiness was described it was typically a decline in practice over time as initial excitement or interest reduced combined with other influences, such as lifestyle changes or a reduced belief in the consequences.

R15/01 carer: I think it's like a lot of things in life, isn't it, you know, you start off, you are very highly motivated and then when you are kind of left to your own devices, it starts to peter out. (LA)

Some carers of low adhering participants described different levels of intent between themselves and the patient, with the carer encouraging more practice. The social pressure carers applied appeared to result in individual practice sessions, rather than sustained practice. For one patient-carer dyad the mismatch in intent resulted in conflict, potentially indicating the importance of the PWA expressing their own interest in engaging with aphasia computer therapy.

R19/19 carer: Now and again I think she found it in herself like, 'oh I don't want to do this today', and it would cause-, well we might have a bit of a row. I'd say, 'come on mam you've gotta do this, you've gotta', and she would, 'no', she didn't want to know. (LA)

Automatic motivational factors were also described, such as emotions, personality, habit and reinforcement. Carer participants, particularly those of low adhering patients, perceived that the emotions experienced by the PWA, particularly their mood and attitude on each individual day, played a significant role in their decision to practice. High adhering participants described personality traits, such as determination and perfectionism, that positively influenced their engagement.

R19/19 carer: But when she had a good day you could see she was happier and she was just 'bom', she'd go through [the exercises] no problem. (LA)

R06/01 carer: He's so determined and so-, if he sets his mind to something he wants to do it and wants to do it really well. (HA)

Most of the high adhering participants described developing a routine pattern of practice which resulted in a habit being formed thus increasing the automaticity of the behavior. The routine either involved doing it every day at the same time or having a regular trigger, for example PWA's spouse watching a television drama in the evening or imitating the working week.

R10/37: I just thought I was doing a job and I just did it like a job. So I did it five days, seven days and then I'm back. (HA)

The StepByStep software provides two types of reinforcement: feedback about the amount of practice time completed and feedback on word-finding ability. Participants found feedback about practice time on the color coded calendar (yellow = some practice, but <20 min; green = more than 20 min practice) motivated them to practice for longer.

R11/03: If it comes down and it's got like a yellow thing that's no good, that's about twenty minutes or so, that's no good I've got to get a green. So you've got to be at least half an hour, maybe a little bit over the top for it to actually transmit. (HA)

Participants valued the feedback the StepByStep software provided on naming performance when the voice recognition function was available and on the spelling tasks in the "using writing to cue naming" exercise. In confirmatory responses during the picture selection task, participants felt seeing the results, trying to do better than last time and trying to achieve 100% were factors that motivated them to carry out more practice. Feedback on performance was perceived to be one reason why computer therapy could be more motivating than paper-based exercises provided by SLTs.

R10/02 Carer: The computer was something very real that he could see and, and perform against, or with on a day-by-day basis and that really suited [PWA]'s, um, learning, or the way he, you know, works. [. . .] He could see his performance, he could see he was making improvement. (HA)

Triangulation Findings

The quantitative data yielded four factors potentially associated with adherence to asynchronous tele-rehabilitation for aphasia, compared to 21 factors identified in the qualitative data. The more comprehensive qualitative data was used as the basis of the "following a thread" method. The convergence coding matrix is presented in **Table 5**.

Qualitative and quantitative findings about patient's capability to use the computer therapy were either complementary or there was silence in the quantitative data. The vital role assistants/volunteers played in enabling participants to develop the skills required to be physically capable of using the tele-rehabilitation exercises was recognized in the qualitative interviews. This complemented the quantitative finding that more assistant/volunteer support was associated with greater adherence in the square root analysis, by providing a possible explanation for why more support might lead to greater adherence. The psychological capability of participants to adhere to regular computer therapy practice was perceived to have been impeded by cognitive impairment and fatigue, both of which can improve over time, which could potentially provide an explanation for the quantitative finding that people were more adherent the more time had passed since their stroke.

Findings relating to the patient's opportunity to engage in practice were either complementary, silent and in one instance, the qualitative and quantitative findings converged. In itself, the passing of time since a patient's stroke is unlikely to have resulted in greater adherence. It is more likely a proxy for recovery, as described above, or lifestyle changes that have taken place over time. Some of the barriers to practice which reduced the participants' physical opportunity to practice included having other commitments or engaging in other therapeutic activities. It is possible that participants might have fewer other commitments or less opportunity to engage in alternative therapeutic activities, the more time that has elapsed since their stroke, thus reducing some of the barriers identified in the qualitative interviews. Another factor perceived to reduce participant's physical opportunity to practice was problems with the computer therapy software and computer hardware, both of which resulted in the computer therapy being available to the participant for less time. This provides a possible explanation for why the length of time the computer therapy was available to participants was significantly associated with adherence in the quantitative findings. The broad consensus from the qualitative data was that high adhering participants perceived greater availability of support (from both therapists and assistants/volunteers) enabling more practice. Some low adherers who perceived they did not have enough support felt they would have been able to practice more if they had increased support. This finding demonstrates convergence with the quantitative findings that the therapist (and possibly the assistant/volunteer) spending more time supporting the participant was significantly associated with greater adherence. The same quantitative finding that more support from therapists and assistants/volunteers facilitated more practice was also complementary in terms of the qualitative finding that external support was perceived to be more beneficial due to the social pressure created by that support not being provided by someone well known to them. This demonstrates the importance of providing "outside" support rather than relying on family carer support.

None of the quantitative data collected corresponded with any of the factors relating to motivation from the qualitative dataset meaning there was silence across all factors associated with motivation.

DISCUSSION

This mixed methods study explored the factors associated with adherence to self-managed aphasia therapy on a computer. Quantitative findings suggested greater adherence is associated with more time having elapsed since the patient's stroke, the patient having access to the computer therapy for longer and the therapist spending more time supporting the participant. Findings from the qualitative interviews were grouped into three themes informed by the COM-B system (18): capability, opportunity and motivation. Factors identified as being associated with the patient's capability to adhere to aphasia computer therapy practice included: cognitive impairment, fatigue, level of understanding of their own condition, knowledge of the intervention, and therapy assistant/volunteer's help to develop the skills required to use the computer therapy. Factors that positively influenced PWA's opportunity to practice included receiving more support from therapists and volunteers/assistants and specific features of the software used (home-based therapy and personalization). Conversely, factors that negatively influenced PWA's opportunity to practice included software and hardware problems, illness, and having other commitments. Motivational factors that influenced adherence comprised PWA's beliefs about their own capability, beliefs about the likelihood of improvement, stability of intentions, reinforcement (via feedback from software), and habit. Triangulation demonstrated several complementary findings in which the qualitative data provided possible explanation for the quantitative findings, but also a lot of silence as the quantitative data were collected for the purposes of the Big CACTUS trial. The triangulation also identified convergence between the two datasets for the finding that people were more engaged with practicing their asynchronous tele-rehabilitation exercises when they received more support from SLTs, providing cross-validation for this finding.

Qualitative interviews highlighted the benefit of on-going support from both SLTs and volunteers/assistants, including the social pressure exerted by external support, the importance of support to enable the patient to develop skills to use the computer therapy and the absence of support being suggested as a reason for low adherence. The amount of time spent by the therapist supporting, monitoring, and adapting the software was found to be predictive of adherence to aphasia computer therapy. Similar findings were identified in a study investigating adherence to home-based exercise programs for neck and low back pain in which patients who received frequent supervision of their exercises had higher levels of adherence (35). Whilst only identified in the square root model and thus to be interpreted

TABLE 5 | Convergence coding matrix.

Elements from the COM-B system used to frame integration	Factors associated with adherence identified through interview data	Factors associated with adherence identified through secondary data analysis of Big CACTUS trial data	Convergence assessment (34)
Physical capability	↕ Ability to use computer therapy software	N/A	Silence
	↑ Assistants/volunteers helped PWA to develop the skills required to use the computer therapy	↑Assistant/volunteer spending more time supporting the participant	Complementary
Psychological capability	↕ Knowledge of recommended practice time	N/A	Silence
	↕Understanding/knowledge of own condition	N/A	Silence
	Cognitive impairment and fatigue (↓forgetting; ↓concentration problems; ↓fatigue; ↑strategies to overcome)	↑Longer length of time post stroke	Complementary
Physical opportunity	Features of the software that facilitated more practice (↑ personalization of vocabulary; ↑therapy in home environment; ↑ independence HA only)	N/A	Silence
	Barriers to practice (↓periods of illness; ↓other commitments; ↓engaging in alternative therapeutic activities)	↑Longer length of time post stroke	Complementary
	Computer therapy software problems (↓issues with voice recognition; ↓stability of the software; ↑stability of the software was improved via software updates) ↓Computer hardware problems	↑Computer therapy available for longer	Complementary
	Availability of support (↑more input from supporters; ↑informal carers of participants who could not use computer therapy independently)	↑Therapist spending more time supporting the participant ↑Assistant/volunteer spending more time supporting the participant	Convergence
Social opportunity	↑ External support (importance of input from SLT or volunteer/ assistant)	↑Therapist spending more time supporting the participant	Complementary
	↑ Social pressure (caused by impending visit from supporter)	↑Assistant/volunteer spending more time supporting the participant	
Reflective motivation	Beliefs about capability	N/A	Silence
	Beliefs about consequences	N/A	Silence
	Goals	N/A	Silence
	Stability of intentions	N/A	Silence
	Differing intention between PWA and carer	N/A	Silence
Automatic motivation	Emotion	N/A	Silence
	Personality	N/A	Silence
	Habit	N/A	Silence
	Reinforcement	N/A	Silence

↓, factor associated with less practice; ↑, factor associated with more practice; ↕, factor associated both with more and less practice.

with caution, the finding that assistant/volunteer support was associated with more practice time echoed findings from the CACTUS pilot study. Most of the participants in the pilot study (3/4) who did not carry out the recommended amount of practice had not received contact from volunteers (36). These findings are indicative of the beneficial impact on-going support and monitoring can have on patient adherence to aphasia computer therapy. This need for support needs to be taken into consideration by those recommending self-managed therapies as a low-cost option. However, the Big CACTUS trial confirmed that the StepByStep computer therapy approach for the NHS is still a low cost option compared to providing the same amount of therapy face-to-face, despite the need for SLT/assistant time in set-up, personalization, and support. The Big CACTUS trial also identified that the intervention was more likely to be cost-effective for patients with mild-moderate word finding difficulties than those with severe word finding difficulties (17).

One of the reasons for attempting to deliver aphasia therapy in a self-managed computerized form is to enable the provision of speech and language therapy in the longer term post-stroke as evidence has demonstrated the effectiveness of such provision (>6 months) (5). Despite evidence of effectiveness, it has been established that PWA in the UK receive less face-to-face SLT the more time that has passed since their stroke (6). The finding that length of time post stroke was associated with greater adherence suggests that the intervention is possibly better suited to those in the longer-term post stroke. In the initial aftermath of a stroke there is a lot of change both mentally, in terms of psychological adjustment, and physically, in terms of receiving other care and rehabilitation interventions. The increased tolerance/adherence could be due to the PWA having more time to focus on therapy or due to a greater understanding of their condition.

Engaging with asynchronous tele-rehabilitation, such as self-managed aphasia computer therapy, requires behavior change. The COM-B system informed the development of the interview schedule and subsequently provided a useful structure upon which to frame the findings from the qualitative interviews and subsequently the convergence coding matrix. COM-B forms the hub of the Behaviour Change Wheel, which also identifies intervention functions that can be incorporated or adapted to enable an intervention to effect behavior change (18). The functions relevant to this tele-rehabilitation intervention include: incentivization, education, training, environmental restructuring, and enablement. We have considered how the functions of the intervention could be adapted to increase the amount of practice carried out by PWA based on the findings of this study. Feedback provided by the aphasia therapy software provided an incentive to practice. Auditory feedback and knowledge of performance, as were provided by the StepByStep software, have been found to be associated with improved performance in stroke rehabilitation more broadly (37). Visual feedback on the amount of practice carried out motivated more practice; however, feedback on performance was only perceived to be motivating when the feedback was accurate. When the voice recognition failed to recognize correct responses, it resulted in frustration and reduced motivation to practice. Improvement of the voice recognition by the software developers would increase the reliability of this incentive thus increasing automatic motivation. The software developers have already started to address this issue, and improvements to the voice recognition have been included in software updates.

The only finding from the triangulation for which qualitative and quantitative data converged was the finding that more support was associated with more practice. Therapists and assistants/volunteers were responsible for training and educating participants about the intervention. Having more time to provide training and education would have the potential to target multiple elements of the COM-B behavior change system through developing the skills to use the computer therapy (i.e., physical capability), increasing knowledge of recommended practice time (i.e., psychological capability), and knowledge about the potential consequences of the intervention (i.e., reflective motivation). Therefore, a clinical recommendation would be to ensure sufficient therapist and assistant/volunteer time is available and intervention development work could include amending training materials to reflect the importance of helping PWA to understand the intervention, the potential benefits and develop the necessary skills to use the computer therapy. A study by Cherney also highlighted the importance of SLT oversight when evaluating the delivery of an asynchronous tele-rehabilitation intervention called Web-ORLA™, although the support in that study was delivered by a virtual therapist rather than home visits (38). In addition, a recent review found that social support and therapist guidance were key factors contributing to adherence to home based exercise practice (39). Environmental restructuring (e.g., extended loan periods/installing software on the participant's own device) and enablement (prompt input from therapists and assistants/volunteers and software developers to reduce the impact of software and hardware problems) are both functions that could be targeted to increase the physical opportunity to practice. Furthermore, targeting the therapy to those participants who had their stroke a longer time ago might enable more therapy by reducing potential barriers highlighted by some participants in the qualitative interviews such as engaging in other therapies or having too many other commitments.

CLINICAL IMPLICATIONS

Clinicians delivering computer therapy should consider the capability of participants to use the computer therapy, including factors such as, cognitive impairment, understanding of their condition, knowledge of the intervention and the role supporters can play in skill development. Furthermore, PWA might have more capability and opportunity to use the computer therapy once more time has passed since their stroke. Clinicians play a vital role in providing the opportunity to practice, which was as much about the need for support from SLTs and volunteers/assistants as it was about ensuring the computer therapy was available for a long period. One of the key roles of the supporters was to provide technical support, which was required to overcome the technological issues with the computer therapy highlighted in this study. Additionally, specific features of therapy software should be considered in relation to the opportunity they provide for practice, with the ability to use the software in their own home and the personalization of practice vocabulary being highlighted as beneficial for the StepByStep software. Clinicians should also consider how the motivation of the PWA might influence their decision to practice, with potentially modifiable motivational factors including creating shared goals and beliefs about the computer therapy, ensuring feedback on performance from the computer therapy is accurate as possible (or not selecting options that do not provide adequate feedback), and helping the PWA to develop a practice routine.

FUTURE RESEARCH

We know that higher doses of aphasia therapy have been found to be more effective (3) and more therapy is being delivered remotely, particularly in response to COVID-19 (40).

Consequently, the need to understand more about who can best engage with computer based therapies and how we can support them to adhere to technology based therapies has never been so great. More research is needed to explore the factors associated with adherence to other computer based therapies to establish whether our findings are more widely applicable. In addition, the qualitative interviews highlighted the importance of motivational factors; however, more research is needed to find quantitative measures of motivation applicable for use with people with aphasia. The findings from this research will also feed into the iterative process of intervention development of the StepByStep approach and future research will be required to evaluate any changes made on the basis of these findings.

STRENGTHS AND LIMITATIONS

This novel study is the first in depth exploration of adherence to self-managed aphasia computer therapy. The mixed methods approach found no divergent findings, facilitated cross-validation where findings converged, and a more comprehensive understanding of the findings when they were complementary. Utilization of Big CACTUS trial data in the secondary data analysis section afforded some advantages including rigorous data collection processes and a relatively large sample size for this hard to reach population. However, the limitation of using data collected for the purposes of the trial meant that important variables relating to adherence, identified in the qualitative interviews, were not measured quantitatively as the variables available were designed for the reporting of the RCT and not designed specifically for the exploration of adherence. This may explain the regression model only accounting for 29% of the variation in practice time. It is possible the model would have benefitted from the inclusion of variables such as self-efficacy (41), intrinsic motivation (42), cognitive ability (particularly executive function, which has been found to be predictive of rehabilitation participation) (43), and technology proficiency. However, finding valid quantitative measures of these variables that are accessible to PWA would be a challenge. The mean length of time between the end of the intervention period and the qualitative interviews being conducted (∼8 months) might have impacted upon participants' ability to recall and reflect on the factors that influenced their adherence. However, it is worth noting that 61% of participants continued to use the computer therapy software beyond the 6-month intervention period, albeit without volunteer/assistant support (17).

Two of the factors found to be associated with adherence to aphasia computer therapy in the quantitative analysis were intervention variables: therapist time supporting the participant and length of access to computer therapy. Results from the intervention variables must be interpreted with greater caution than the demographic and clinical variables as they are not time dependent and it is possible that the amount of practice completed could have influenced the amount of support provided or length of access, rather than the other way round. There was a high variability (indicated by high standard deviations throughout), a positive skew and some outliers (particularly high adhering participants) in the dependent variable. Regression can be particularly sensitive to outliers, but as there was no evidence that the data were inaccurate outliers were not removed. The square root sensitivity analysis reduced the variability, the skew and the impact of outliers, thus improving the normality of the data (44). The process of bivariate testing used to select variables for inclusion in the regression model is criticized by some statisticians for increasing the likelihood of an "overfitted" model with an increased risk of a type I error (45). However, due to the lack of prior research around predictors of adherence to speech and language therapy interventions for aphasia there was no prior evidence or theory upon which the decision of which factors to include could be made. Conclusions must be interpreted in light of the fact that this was exploratory research.

Considerably more male PWA (83%) were recruited to the qualitative interviews. The Big CACTUS trial had a slight male gender bias 60% (17); contrary to a recent review which found that aphasia rates are higher in women (46). The increased gender difference in this sample compared to the wider Big CACTUS sample might have been due to self-selection or it might have been the result of using a maximum variation sampling strategy as it might have been that women were more often moderate adherers.

CONCLUSION

Amounts of self-managed practice of aphasia therapy exercises on a computer are hugely variable from person to person. This exploratory mixed methods study highlighted a number of factors found to be associated with adherence to self-managed aphasia therapy on a computer. Clinicians delivering this asynchronous tele-rehabilitation intervention should consider the factors highlighted in this study relating to capability, opportunity and motivation when deciding which patients may be most likely to engage with this mode of treatment, as well as how they can be supported to optimize the amount of practice they engage in.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical approval for the secondary analysis was obtained from Leeds West Research Ethics Committee (REC; 13/YH/0377) and the Scottish A REC (14/SS/0023). Separate approval for the qualitative interviews was obtained from the School of Health and Related Research REC at the University of Sheffield (008063).

AUTHOR CONTRIBUTIONS

MH, RP, and CC contributed to conception and design of the study. MH performed the statistical analysis, collected the qualitative data, coded the qualitative data, and wrote the first draft of the manuscript. All authors contributed to the interpretation of the qualitative data and contributed to the article and approved the submitted version.

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Analysis of Feasibility, Adherence, and Appreciation of a Newly Developed Tele-Rehabilitation Program for People With MCI and VCI

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Background: Patients with Mild Cognitive Impairment (MCI) and Vascular Cognitive Impairment (VCI) are at a high risk of progressing to dementia. Recent guidelines indicate the importance of promoting multidimensional and multi-domain interventions to prevent further decline. Due to its growing effectiveness, comparable to conventional face-to-face interventions, the use of technology is gaining relevance. Tele-rehabilitation systems have the potential to engage patients in multi-dimensional activity programs and to guarantee a low-cost continuum of care through remote control. A possible limitation of such programs is represented by the lack of familiarization with technology and computers in elderly people. The purpose of this study is to describe the feasibility, adherence, and appreciation of the GOAL Tele-R system, administered by a web-application through remote control in patients with MCI/VCI.

Methods: Feasibility of the Tele-R system was evaluated by means of distribution of patients' attrition along the study phases, controlling for potential systematic bias in drop-out rates due to the technological device. Adherence was evaluated analyzing drop-out rates and indexes of carried out activities. Patients' appreciation was analyzed through *ad hoc* satisfaction questionnaire items.

Results: Out of 86 approached patients, 25 (29%) were not enrolled, 30 (35%) dropped-out after randomization, and 31 (36%) completed the study (standard care group $n = 12$, the tele-R group $n = 19$). Compared to the tele-R group, rates of drop-outs resulted significantly higher for the standard care group (34 vs. 62%, respectively, $p = 0.029$). Taking into account baseline characteristics, females resulted in a statistically significant higher rate of drop-outs compared to males (66 vs. 27%, respectively, $p = 0.003$). Overall adherence to the proposed activities was 84% (85% for cognitive module and 83% for physical activity module). Concerning satisfaction, participants provided a good mean level of appreciation (3.7 ± 0.8, range 1–5), a positive feedback for usability, and a subjective perception of cognitive, emotional, and physical benefits due to the training.

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Conclusion: The GOAL Tele-R system seems a feasible technological rehabilitation program, reaching an acceptable level of adherence and appreciation in patients with an MCI/VCI condition.

Clinical Trial Registration: www.ClinicalTrials.gov, ID: NCT03383549 (registration date: 26/dec/2017).

Keywords: mild cognitive impairment, vascular cognitive impairment, tele-rehabilitation, efficiency, web application

INTRODUCTION

Mild Cognitive Impairment (MCI) is a clinical syndrome that includes persons who do not fulfill a diagnosis of dementia, but who have a high risk of progressing to a dementia disorder (1). This diagnosis describes a prodromal or transitional state whereby individuals present reduced performances on selected neuropsychological tests with spared autonomies in basic and instrumental activities of daily living (1, 2). Furthermore, cerebrovascular diseases could lead to a vascular cognitive impairment (VCI), which represents a high-risk stage to develop vascular dementia (3).

No effective disease-modifying treatments are available for patients with MCI/VCI, and the most recent guidelines indicate the importance of promoting multidimensional and multi-domain interventions to prevent cognitive decline (4). A multidimensional program is characterized by the integration of different activities such as the combination of motor and cognitive activities (5). A cognition-focused intervention could involve training typically based on a set of standard tasks designed to train cognitive functions (6). The tasks may be structured according to a multidomain intervention paradigm to exercise memory, attention, language, and/or executive functions (6–8).

Evidence has shown that MCI/VCI patients who underwent cognitive training reported changes in brain activation patterns and increased connectivity between brain regions (9, 10). A meta-analysis (11) supported a significant role in MCI/VCI for physical activities to counteract cognitive decline, for all levels of physical activity. Finally, prospective studies demonstrated that socially stimulating activities could have a protective effect against dementia (12). In this regard, studies reported that the association of a cognitive, physical and social stimulation could represent a promising multidimensional intervention for patients with MCI/VCI to contrast dementia onset (13–15) and for patients with mild AD to improve cognitive-behavioral status by restoring the neural functioning (16). Unfortunately, these results can be obtained through intensive face-to-face sessions that are sometimes cost-demanding and unlikely implementable on a large scale (17). Because of its comparable effectiveness to conventional interventions, the use of technology to assist persons at risk or with early dementia is gaining relevance (17, 18). In recent years, a considerable amount of research has focused on the development of low-cost and home-based tele-rehabilitation systems to provide rehabilitation programs (19). Tele-rehabilitation may represent an effective method to gain patients' engagement and to guarantee a low-cost continuum of care through remote control (17, 20). In fact, this kind of service supplies distant support, information exchange between patients and their clinical providers and promotes the administration of multi-dimensional activity programs (20, 21). However, a possible limitation of such programs is represented by the risk of a low adherence to the treatment, due to the lack of familiarization with technology and computers in elderly people (18, 20, 22–24). In the framework of tele-rehabilitation interventions in patients with MCI, several studies have proposed the possibility to provide a tailored intervention, both in its intensity and duration (17, 18), focused on cognitive training (25, 26). Recent reviews investigated the feasibility and acceptability of telemedicine programs in older adults, finding overall positive results (27, 28). However, only a few studies were focused on the feasibility and the acceptability of a remotely delivered cognitive rehabilitation for persons with early AD (29, 30) or mild cognitive impairment (30, 31). Narasimha and Colleagues reviewed 16 usability studies among geriatric patients, suggesting overall good feasibility and usability. However, in this review, no Italian studies were included, and only one was specifically focused on patients with MCI showing several limitations (e.g., small sample size, MCI mixed with mild dementia) (28).

In Italian setting, tele-rehabilitation studies among older patients are mainly focused on healthy aging, to promote an improvement in quality of life (32–34) or on geriatric demented patients (35). Despite the existence of recommendations for the use of serious games in MCI (36, 37), to date evidence of Italian studies reporting a specific analysis of the feasibility and the adherence of tele-rehabilitation training in MCI/VCI is missing. To investigate the beneficial effects provided by both cognitive, physical and social activities, the Games for Older Adults' Active Life ("GOAL Tele-R" project) was created. Particularly, the GOAL Tele-R project aimed to propose the use of a user-friendly web application developed through a co-participatory design (38) involving patients with MCI/VCI, clinicians, technicians, and caregivers. This article is aimed at reporting data on feasibility, adherence and appreciation of the GOAL Tele-R system administered by a web-application through remote control in patients with MCI/VCI. The analysis of the effectiveness of Tele-R is not part of this work, and it is still under evaluation.

MATERIALS AND METHODS

The GOAL (Games for Older Adults' Active Life) Project is a randomized controlled clinical trial. The study methods and protocol have been previously published in detail (23). According to the inclusion criteria, eligible participants have been assessed through a baseline extensive evaluation including cognitive, behavioral, functional, and perceived quality of life measures [to see the detailed evaluation, see Fabbri et al. (23)]. Among the scales included in the baseline protocol, the following have been used in the present study:

- Montreal cognitive assessment (MoCA), as a global cognitive functioning screening tool (39);
- Free and Cued Selective Remainding Test (FCSRT);
- Digit Span forward and backward;
- Corsi Span forward and backward;
- Rey Complex Figure Test;
- Modified card sorting Test;
- Trail Making Test Part A and B;
- Stroop Test;
- Phonemic Fluency;
- Semantic Fluency.
- Activities of Daily Living Inventory (ADCS/ADL), to assess the patient's level of autonomy in the basic and instrumental activities of daily living;
- Center for Epidemiological Studies Depression scale (CESD) to evaluate depressive symptoms;
- Physical and mental component summary scores of the 36-Item Short Form Survey (SF-36) to assess the subjective perceived quality of live.

Subsequently, through the use of a computer algorithm (http://www.graphpad.com/quikcalcs/randMenu/), patients have been randomly assigned to the control or treatment group. The control group received a standard care (12 months follow-up visit). The treatment group performed, for 8 weeks, cognitive exercises 3 days a week, Adapted Physical Activities (APA, 40) 2 days a week, and social activities once a week, administered through a tablet. Immediately at the end of treatment, subjects underwent a post-training assessment including the administration of an *ad hoc* satisfaction questionnaire. The latter was developed in order to evaluate the following issues:

- experience appreciation (range: 1–5, where 5 indicated a very high appreciation);
- preference module;
- usability (Yes/No);
- perception of physical benefits (Yes/No);
- perception of cognitive benefits (Yes/No);
- perception of emotional benefits (Yes/No);
- satisfaction for the variety of exercises (Yes/No).

Both the experimental and the control group received a comprehensive neuropsychological and physical evaluation after 12 months.

The study was conducted according to the Declaration of Helsinki principles and was approved by the Local Ethics Committee. All data were collected from the IRCCS Don Carlo Gnocchi Foundation.

Participants

Participants were recruited from the Memory Clinic of University Hospital of Careggi, (Florence, Italy) and from the Don Carlo Gnocchi Foundation (Florence, Italy). Participants were included in the study if they fulfilled core criteria for MCI (1) or VCI (3), based on clinical, neuroimaging, and neuropsychological information. Additional inclusion criteria were: (1) Mini Mental State Examination (MMSE) score >24; (2) age between 65 and 80 years old; (3) school attendance >3 years; (4) right-handed according to the Edinburgh Scale (40); (5) Italian language as mother tongue; (6) normal or corrected visual and auditory acuity; (7) preserved physical mobility or manual dexterity. According to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) and the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria (41, 42), patients with mild dementia were excluded. Other exclusion criteria were: intellectual deficiency, alcoholism or toxicomania, use of psychotropic medication known to impair cognition, presence or history of severe psychiatric disorders, presence or history of stroke, presence or history of a neurological disorder, and general anesthesia in the last 6 months. During the initial contact, the details of the study were explained and only individuals who agreed to participate for the duration of the study were retained. All participants signed a consent form prior to participation in the study.

Tele-R Program: GOAL-App

The GOAL-app is a newly designed web-application (23, 43) that includes an *ad-hoc* weekly program that combines cognitive, physical, and social activities. The detailed explanation has been published in Martini et al. (34).

The first web-app prototype was implemented through a series of design and feedback loops with MCI/VCI specialists, patients with MCI/VCI and their caregivers. Before the beginning of the 8-weeks program, participants were trained to use the provided tablet autonomously by a multidisciplinary team.

The planning and the monitoring of each activity were accessible by the clinical team through the admin interface of the app. Each activity was implemented in three independent modules (**Figure 1**):

➢ The cognitive module integrated cognitive exercises from BrainHQ, a third-party platform developed by Posit Science [Posit Science Corporation, San Francisco, CA (44)]. Participants performed these exercises 3 days per week.
➢ The physical module included a training program of APA exercises (45), delivered through a guided video, to be performed 2 days per week.
➢ The caregiver module included suggestions on social activities to be carried out with the caregiver during the

weekend. Patients were suggested to carry out one activity per week.

Statistical Analysis

Feasibility of the Tele-R system was evaluated by means of distribution of patients' attrition from the screening phase to follow-up assessments (excluded and drop-out rates). In order to control for potential systematic bias due to the technological device, comparisons between patients that completed the study and drop-outs will be carried out for baseline characteristics (demographics, global cognitive and functional status, neuropsychological test scores, mood, and quality of life)

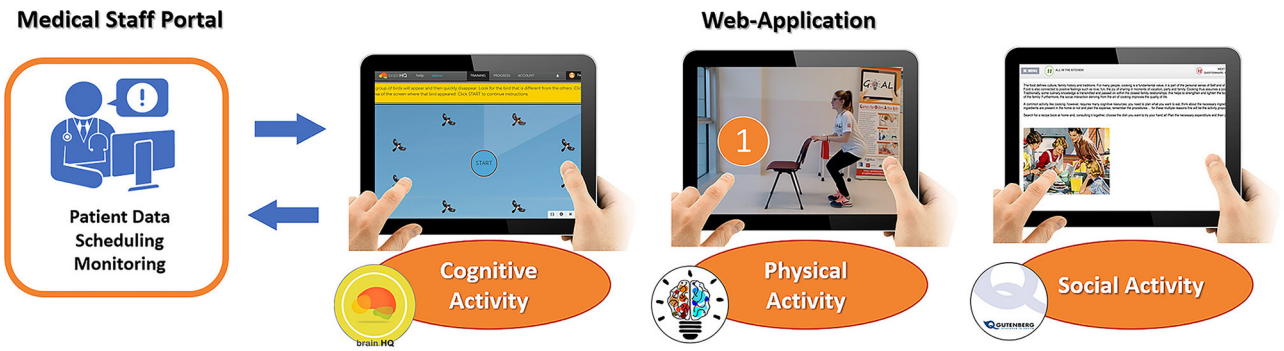

FIGURE 1 | Functional architecture of GOAL-App.

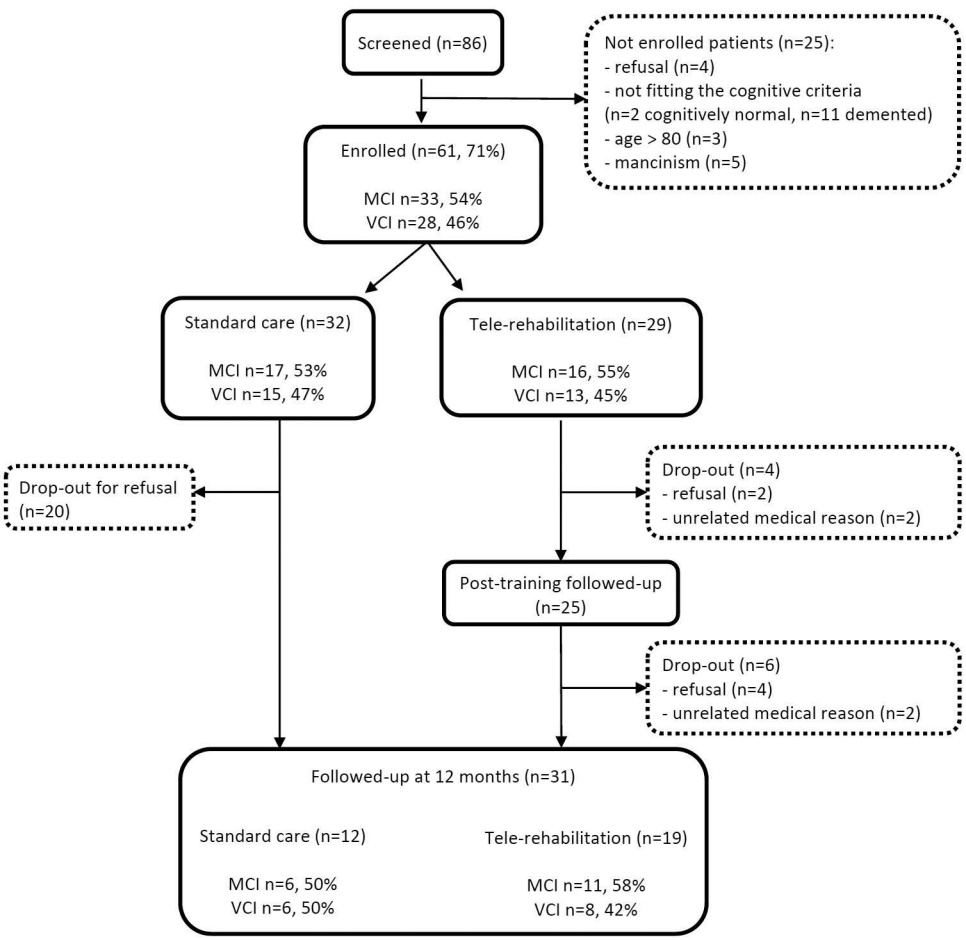

FIGURE 2 | Flow diagram representing patients' attrition from the screening phase to follow-up assessments.

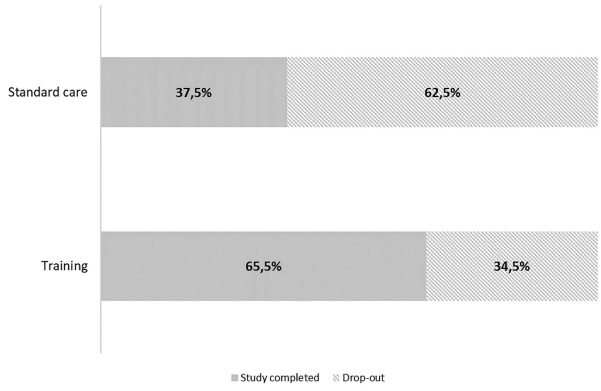

FIGURE 3 | Drop-out distributions according to treatment groups ($\chi^2 = 4.778$, $p = 0.029$).

by means of univariate analyses (Mann-Whitney *U*-tests and chi square tests).

Adherence to the Tele-R system was evaluated comparing drop-out distributions according to treatment groups (chi square test), and showing percentages and means of a rehabilitation adherence score (AS) of carried out activities (cognitive, social, and physical) within the treated group.

Patients' appreciation of the Tele-R system was analyzed through descriptive statistics of the *ad hoc* satisfaction questionnaire items.

RESULTS

Flow diagram representing patients' attrition from the screening phase to follow-up assessments is reported in **Figure 2**. Eighty-six persons were contacted to enter the study, and 25 (29%) were not enrolled due to the following reasons: refusals ($n = 4$), not fitting the cognitive criteria (cognitively normal $n = 2$, demented $n = 11$), age >80 years ($n = 3$), and mancinism ($n = 5$). Of the remaining 61 patients, 32 (52%) were randomly assigned to the standard care group and 29 (48%) to the tele-R group. Among the standard care group, 20 (62.5%) patients dropped-out and refused to undergo the 12-month follow-up visit. In the tele-R group, four patients dropped-out during the training period (refusals $n = 2$, unrelated medical reasons $n = 2$), and further six patients completed the treatment and were evaluated at the post-training follow-up visit but declined the 12-month final visit (refusals $n = 4$, unrelated medical reasons $n = 2$).

As shown in **Figure 3**, there was a statistically significant difference in drop-out rates between treated and non-treated patients (34.5 vs. 62.5%, respectively, $\chi^2 = 4.778$, $p = 0.029$). Thirty-one patients (51% of baseline enrolled cohort) completed the final 12-month visit (standard care group $n = 12$, the tele-R group $n = 19$).

Despite the high rate of drop-outs among enrolled patients, as shown in **Table 1** comparisons between patients that completed the study and drop-outs showed not statistically significant differences in baseline demographics characteristics (age 74.2 ± 4.1 vs. 73.6 ± 3.9; years of education 10.3 ± 4.6 vs. 9.8 ± 4.6; global cognitive and functional status (MoCA score 20.9 ± 3.3 vs. 22.6 ± 3.7; ADCS/ADL score 75.2 ± 4.4 vs. 75.2 ± 3.6, neuropsychological data (see **Table 1** for details), mood and quality of life (CESD score 14.9 ± 6.6 vs. 16.6 ± 6.9; physical component summary of SF-36 49.8 ± 9.4 vs. 46.4 ± 8.5, mental component summary of SF-36 45.9 ± 9.7 vs. 43.8 ± 8.3) except for sex. Females resulted in a statistically significant higher rate of drop-outs (66%) compared to males (27%, $p = 0.003$) (**Table 1**). Among the 23 females that dropped out, 17 (74%) were in the standard care group, while 6 (26%) were in the tele-rehabilitation one. Comparisons between males and females showed no statistically significant differences in age (74.6 ± 3.4 vs. 73.4 ± 4.3 years, respectively, $p = 0.229$), years of education (10.6 ± 4.8 vs. 9.7±4.4 years, respectively, $p = 0.437$), baseline MoCA demographically adjusted total score (20.9 ± 3.6 vs. 22.6 ± 3.6, respectively, $p = 0.069$), and baseline depressive symptoms as measured by the CESD scale total score (13.9 ± 5.2 vs. 17 ± 7.5, respectively, $p = 0.076$).

Regarding the "cognitive impairment subtype" variable, it is worth noting that MCI and VCI were balanced between drop-outs and participants who completed the study, at different time point: at the enrollment, at the treatment allocation, and at the study termination (**Table 1**; **Figure 2**).

The overall mean rehabilitation adherence score (SD) for the treated group was 84%. Particularly, participants showed a high adherence to the proposed activities with 85% for cognitive module and 83% for physical activity module (see **Figure 4**). Conversely, only one participant carried out the whole social module, the other participants did not complete any of the activities proposed in this module.

Concerning results of the *ad hoc* satisfaction questionnaire, all participants judged the program as useful and their average level of appreciation of the treatment was good (range 1–5; mean = 3.7, SD = 0.8). As shown in **Figure 5**, 92% of participants reported to be satisfied with the variety of exercises, and 84% gave positive feedback in terms of ease of use. Particularly, 76% of patients reported a subjective perception of benefits regarding cognition, physical wellness, and emotional benefits after the 8-weeks program. Specifically, 60% of participants declared to prefer both cognitive and physical modules, 32% appreciated the cognitive module more, and the remaining 8% the physical module.

DISCUSSION

The proposed GOAL Tele-R system showed encouraging results in terms of feasibility, adherence, and appreciation in our cohort of MCI/VCI patients. Refusal rate was ∼6% of the eligible patients, and drop-out rates resulted significantly higher in standard care than in treated patients, thus the proposed approach seemed not to discourage patients from participating.

Previous studies on the efficacy of a cognitive computer intervention program in patients with MCI reported no drop-out rates within the treated groups (46–48), thus corroborating the hypothesis of an overall good compliance of computer-based

TABLE 1 | Comparisons between patients that completed the study and drop-outs for the baseline characteristics.

		Score range	Study completed *N* = 31	Drop-Out *N* = 30	*p*
Age, years*	mean ± SD	-	74.2 ± 4.1	73,6 ± 3.9	0.563
Years of education*	mean ± SD	-	10.3 ± 4.6	9.8 ± 4.6	0.650
Sex#					
Females	*N*(%)	-	**12 (34%)**	**23 (66%)**	**0.003**
Males			**19 (73%)**	**7 (27%)**	
Cognitive impairment subtype (MCI)#	*N*(%)	-	55%	53%	0.906
Montreal Cognitive Assessment*	mean ± SD	0–30	20.9 ± 3.3	22.6 ± 3.7	0.070
FCSRT Immediate Free Recall*	mean ± SD	0–36	23.7 ± 6.3	24.4 ± 8.2	0.423
FCSRT Delayed Free Recall*	mean ± SD	0–12	8 ± 3.1	8.2 ± 3.9	0.248
Digit span forward*	mean ± SD	3–9	5.8 ± 1.2	5.7 ± 0.9	0.530
Digit span backward*	mean ± SD	3–9	4.3 ± 1.1	4.1 ± 1.1	0.464
Corsi span forward*	mean ± SD	3–9	5.3 ± 1.1	4.9 ± 0.8	0.180
Corsi span backward*	mean ± SD	3–9	4.6 ± 1	4.7 ± 1.1	0.668
Rey Complex Figure Test copy*	mean ± SD	0–36	30.9 ± 8.3	31.8 ± 5.9	0.893
Rey Complex Figure Test delayed recall*	mean ± SD	0–36	14.8 ± 7.5	20.1 ± 18.9	0.375
Modified card sorting Test (*errors*)*	mean ± SD	-	5.8 ± 4.8	7.1 ± 5.7	0.422
Trail Making Test, Part A (*time, seconds*)*	mean ± SD	-	39.1 ± 23.7	44.1 ± 34.1	0.808
Trail Making Test, Part B (*time, seconds*)*	mean ± SD	-	72.7 ± 74.6	58.2 ± 67.1	0.791
Stroop test (*time, seconds*)*	mean ± SD	-	18.1 ± 13.2	25.9 ± 16.6	0.054
Stroop test (*errors*)*	mean ± SD	-	3.4 ± 7	1.9 ± 5.8	0.479
Phonemic verbal fluency*	mean ± SD	-	31.4 ± 11.8	34.3 ± 10.3	0.419
Semantic verbal fluency*	mean ± SD	-	37.5 ± 8.9	35.5 ± 11.6	0.466
Activities of Daily Living Inventory*	mean ± SD	0–78	75.2 ± 4.4	75.2 ± 3.6	0.750
Center for Epidemiological Studies Depression scale*	mean ± SD	0–60	14.9 ± 6.6	16.6 ± 6.9	0.351
Physical component summary (36-Item Short Form Survey)*	mean ± SD	0–100	49.8 ± 9.4	46.4 ± 8.5	0.056
Mental component summary (36-Item Short Form Survey)*	mean ± SD	0–100	45.9 ± 9.7	43.8 ± 8.3	0.344

FCSRT: Free and Cued Selective Reminding Test.
**Mann-Whitney U-tests, #Chi square tests. Bold values represent a statistically significant difference in the distribution of the variable sex between the groups.*

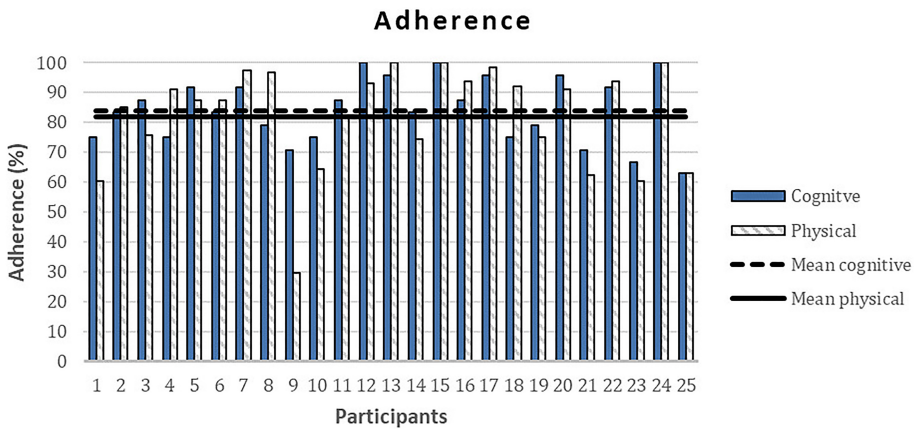

FIGURE 4 | Adherence to the proposed activities in treated subjects.

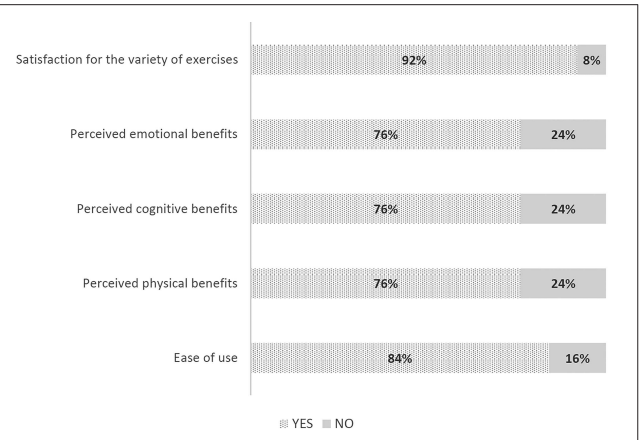

FIGURE 5 | Results of the *ad hoc* satisfaction questionnaire.

cognitive treatments. On the other hand, these training programs were quite short (∼4 weeks), and drop-out rates were likely to increase in studies based on longer computer-assisted trainings. In a study by Belleville and colleagues, a drop-out rate of 15% was reported for an intervention administered in 8 weekly sessions of 120 min each (49).

Compared to these studies, our results showed a higher drop-out rate (34.5% in the tele-rehabilitation group and 62.5% in the standard care group), however, similar value of drop-out in the intervention group was reported by Makai (38%) (24) and De Cola (29%) (34). Causes of discontinuation have been listed in **Figure 2** (refusal/unrelated medical reason). A possible explanation of drop-out in the tele-rehabilitation group may be due to a demanding approach both for the long duration and its multidimensional format. Indeed, a difficulty in introducing elderly people to a new technology, has been reported by other Authors (18, 20, 22, 24, 28, 34). Since normal or corrected visual and auditory acuity was requested at the inclusion, participants did not drop out for disperception. However, it is encouraging that the higher drop-out rate was found in the non-treated group, and that high overall adherence to the training program (84%) was documented for the treated group. It is possible that participants in the control group felt alone in counteracting their cognitive problems and in the absence of a treatment, they felt less motivated to continue the study. A possible solution may be represented by a combination of technical devices and personal interaction with health care professionals, in order to monitor and support patients' adherence to the program (34, 50).

No differences were found in baseline characteristics of drop-outs and participants who completed the study, except for sex. Since the two groups did not show differences in neuropsychological results, the absence of a selection bias based on cognitive status is confirmed. On the other hand, the higher rate of women who dropped out from the program compared to males is interesting and may reflect some gender-specific issue in the study compliance: it is possible that women encountered difficulties in balancing the treatment demands and the management of their role within the family, e.g., household activities. In this regard, no differences were found between males and females on baseline characteristics. Different results were obtained by De Cola and Colleagues in a study aimed at assessing usability and patients' satisfaction of a teleassistance program for frail elderly people. They found that a reduced adherence in the teleassistance program was associated with male gender, older age, urban residence, and with the application of the isolated telemonitoring program, when not associated with the telecounselling through an audio-video conference (34). Differently from the study protocol of De Cola, in our study, a control group was compared to the treated group. Nowadays, web-technologies provide high tailored open sources services and in the proposed work it is possible to observe a good level of appreciation and an overall positive feedback for usability. This is probably due to a deep customization of the web-application. Furthermore, our results showed that patients reported a subjective perception of cognitive, emotional, and physical benefits due to the training. In this regard, Cotelli and Colleagues argue that currently the available evidence is insufficient to draw conclusions about the effects of tele-rehabilitation on cognition, health related quality of life or participant satisfaction, highlighting that the quality of the clinical studies' designs need to be improved. An encouragement to the tele-rehabilitation use comes from a recent review that confirms Virtual-reality technology as a very effective tool for cognitive assessment and recovery in patients with cognitive impairment (51). Moreover, a recent meta-analysis conducted on Exergames (Physically-active video games) concluded that benefits were observed with this kind of treatment for both healthy elderly and clinical populations with cognitive impairments (52).

This study also had several potential limitations. First, patients underwent different types of exercises during the course of the 8 weeks, and some reported dissatisfaction for the variety of proposed activities. To overcome this limitation, an additional integration of other exercises could reduce the repetitiveness. Second, the low adherence to the social module during the weekend might be the result of an over demanding request, whose positive impact was probably underestimated by some of the patients. A possible solution may be to improve patients' engagement and motivational support through a strategy based on periodical "human" contact (e.g., telephone calls, text messages, or email) and feedback (53, 54). Another important limitation of this project is the low level of involvement of the caregiver during the patient's activities. Since caring for a person with cognitive decline may have negative consequences for caregivers, several studies highlight the importance of their support (55, 56), in line with the Chronic Care Model (57, 58). Unfortunately, the comprehensive involvement of the caregiver is often difficult and the use of care technology with caregivers is still limited in daily practice (59, 60). Since follow-up data are not yet analyzed, currently it is impossible to state whether our results on feasibility, adherence and satisfaction of the tele-rehabilitation program have been influenced or not by the progression of the disease. We evaluated adherence and feasibility with objective measures

and satisfaction through an *ad hoc* satisfaction questionnaire. We are confident that these tools are suitable for this scope. However, in this context, a standardized protocol is not yet available.

Taking into account the relatively low costs and easy accessibility of this e-health intervention, the GOAL Tele-R system seems to be an efficient and promising program to take care of patients with MCI/VCI. However, further studies must quantitatively assess the efficacy of this system, in terms of counteracting cognitive decline.

To conclude, the GOAL Tele-R system seems suitable to provide a multidimensional rehabilitation program, and may represent an enabling technology in the healthcare sector that allows a customized person-centered intervention.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Careggi University-Hospital Local Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

IEM, ES, LF, GLu, LB, FB, FV, and CM developed the original concept of the trial. LF, FB, GLu, FV, and CM drafted the original protocol. LF, IEM, FG, SP, GLu, FB, FV, and CM developed the design. IEM, ES, LF, GLu, FB, and CM developed the methodology. ES, IEM, SP, LF, FB, FV, and CM developed the analysis plan. IEM, ES, LF, GLo, FG, FB, FV, and CM adapted the trial proposal as a protocol paper. IEM, ES, LF, SP, FV, GLo, SS, and CM did manuscript writing. All authors reviewed and commented on drafts of the protocol and paper. All authors read and approved the final manuscript.

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Using the Technology Acceptance Model to Identify Factors That Predict Likelihood to Adopt Tele-Neurorehabilitation

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Tele-neurorehabilitation has the potential to reduce accessibility barriers and enhance patient outcomes through a more seamless continuum of care. A growing number of studies have found that tele-neurorehabilitation produces equivalent results to usual care for a variety of outcomes including activities of daily living and health related quality of life. Despite the potential of tele-neurorehabilitation, this model of care has failed to achieve mainstream adoption. Little is known about feasibility and acceptability of tele-neurorehabilitation and most published studies do not use a validated model to guide and evaluate implementation. The technology acceptance model (TAM) was developed 20 years ago and is one of the most widely used theoretical frameworks for predicting an individual's likelihood to adopt and use new technology. The TAM3 further built on the original model by incorporating additional elements from human decision making such as computer anxiety. In this perspective, we utilize the TAM3 to systematically map the findings from existing published studies, in order to explore the determinants of adoption of tele-neurorehabilitation by both stroke survivors and prescribing clinicians. We present evidence suggesting that computer self-efficacy and computer anxiety are significant predictors of an individual's likelihood to use tele-neurorehabilitation. Understanding what factors support or hinder uptake of tele-neurorehabilitation can assist in translatability and sustainable adoption of this technology. If we are to shift tele-neurorehabilitation from the research domain to become a mainstream health sector activity, key stakeholders must address the barriers that have consistently hindered adoption.

Keywords: stroke, neurorehabilitation after stroke, tele-neurorehabilitation, technology—ICT, telehealth acceptance

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STROKE

Great advances have been made in acute stroke management, which has led to a marked decrease in mortality rates (1). However, incidence remains high with almost 14 million new strokes occurring annually and more than 80 million prevalent cases globally in 2016. The annual cost to society for first-ever stroke in Australia is AUD $5 billion and in the United States USD $50 billion and includes hospitalization, informal care and loss of productivity (2, 3).

Stroke is the main cause of acquired disability in the adult population with high numbers of survivors experiencing sensorimotor impairment, reduced cognition, and reduced function (4–7). There is strong evidence showing that neurorehabilitation in the acute, subacute, and chronic phases of recovery improves patient outcomes across numerous domains including activities of daily living and health-related quality of life (8–13). Improvement in function and subsequent reduction of disability, by as little as 1-point on the Modified Rankin Scale (mRS), can reduce the costs of care by 85% (2). Despite the evidence of the effectiveness of neurorehabilitation and the potential to reduce burden of care and associated costs, access to rehabilitation is inequitable. A recent audit of acute stroke care in Australia found that only 39% of patients admitted with a primary diagnosis of stroke were assessed for rehabilitation yet 75% were found to have rehabilitation needs (14). This suggests that a large number of Australian stroke survivors may be missing out on the opportunity to maximize their recovery. An Australian study exploring rehabilitation referral patterns for stroke survivors found there were significant variations in selection resulting in inequitable access to rehabilitation (15–17). The reasons for the variation in referrals for neurorehabilitation are multiple and include clinical and non-clinical factors such as reduced workforce capacity and limited access to rehabilitation beds requiring a prioritization approach (17).

Factors that impact on the provision of specialize neurorehabilitation are common across both developing and developed countries (14–18). In Australia, funding models typically emphasize reducing length of stay in an effort to reduce the cost of an episode of rehabilitation. In developing countries, access to organized stroke care, particularly neurorehabilitation, is limited (1, 19, 20). The need for alternative models of neurorehabilitation that are effective and efficient and can overcome current barriers has become an urgent priority, particularly in the more recent context of the COVID-19 pandemic where the demand for remote healthcare has increased rapidly. Telehealth strategies have shown great potential globally as an effective strategy to improve accessibility to healthcare (21, 22). Neurorehabilitation delivered using a telehealth platform, known as tele-neurorehabilitation, may overcome some of the barriers evident in more traditional, center-based models of care. This is particularly true for low and middle-income countries where access to specialized health and rehabilitation services is limited but information and communication technologies (ICT) are readily available and commonly used (23).

TELE-NEUROREHABILITATION

Tele-neurorehabilitation refers to a model of care that uses ICT to deliver clinical rehabilitation and education to patients with a neurological condition at a remote location, such as the patient's home (24, 25). There is a broad range of ICT that may be used in tele-neurorehabilitation from simple devices such as telephones and videoconferencing, up to more complex sensor-based systems with inertial measurement units (25–28).

The number of studies exploring effectiveness of tele-neurorehabilitation has grown over the last 10 years. This increased focus reflects advances in ICT and the growing need to find efficient, effective and economical models of care in the context of fiscally constrained healthcare settings. Laver et al. recently completed a systematic review of tele-neurorehabilitation for stroke services which included evidence from 22 randomized controlled trials with a total of 1,937 participants (29). The studies encompassed a large range of interventions such as mobility retraining, communication therapy and upper limb programs. The technologies used were equally varied and included telephone follow ups, electrical stimulation, IMU sensors and a virtual online library. The authors of the review found there was moderate-quality evidence that tele-neurorehabilitation for stroke survivors achieves results equivalent to usual care for activities of daily living, depressive symptoms, and health related quality of life. However, Laver et al. noted that the studies included in the systematic review did not address feasibility of ICT from the perspective of either the participants or the prescribing clinicians. This raises questions regarding what type of patient is most appropriate for a tele-neurorehabilitation program, how much training is needed for both user and prescriber and what infrastructure is necessary to support sustainable implementation of this model. The large body of research on implementation science suggests that a theoretical model can provide a framework to guide both implementation and evaluation of tele-neurorehabilitation and potentially enhance sustainable adoption of this model (30).

TELE-NEUROREHABILITATION AND TECHNOLOGY ACCEPTANCE

The technology acceptance model (TAM) is one of the most widely utilized theoretical models explaining an individual's intention to use new technology (31, 32). The first iteration of the TAM was developed in the 1980's and proposed that a person's intention to use and subsequent use of technology can be predicted two beliefs: (1) their perception of how useful the technology is, and (2) their perception as to whether it is easy to use. A large body of research on the TAM found that it consistently predicted 40% of the variance in the intention to use and subsequent use of technology (31). Twenty years later, the TAM was extended to become the TAM2 and included output quality, results demonstrability, job relevance, subjective norm and perceived ease of use as determinants of perceived usefulness. Another model, the determinants of perceived ease of use, was developed at the same time and included factors that anchor beliefs about technology, including computer self-efficacy, computer anxiety, computer playfulness and perceptions of external control (31). Furthermore, experience and voluntary use of the technology were considered to be factors that moderated perceived usefulness.

Most recently, the TAM2 and the determinants of perceived ease of use have been combined to become the TAM3. This integrated model proposes that perceived usefulness is influenced by a number of factors including the quality of output from

the technology and how relevant it is to the needs of the user. Perceived ease of use is determined by the person's beliefs about their own skills and includes computer self-efficacy and anxiety. Importantly, both perceived usefulness and perceived ease of use can be mediated through external factors such as increased practice / experience using the technology and adequate resources to support the person's use of technology (31).

There is a significant body of research on application of all iterations of the TAM in health settings, particularly in relation to the adoption of electronic health records and telehealth (33, 34). A recent study used the TAM to predict if a group ($n = 325$) of Canadians would use electronic medical health records to manage health information such as making future appointments (35). The authors found that perceived ease of use was the strongest predictor of perceived usefulness. The users' prior experiences with technology, needs and values all correlated with intention to use the electronic medical health record. Another study exploring patient uptake of electronic health records found that difficulties logging in and a complex user interface impacted on adoption (36). Despite the growing evidence-base using the TAM to predict user adoption of technology, none of the published studies focus on tele-neurorehabilitation. The aim of this perspective is to explore if published studies on tele-neurorehabilitation can be mapped onto the variables in the TAM3.

METHODS

A systematic mapping review approach was selected as the intention was to describe and categorize the body of tele-neurorehabilitation evidence using the TAM3 framework. A traditional systematic review aims to identify and assess the quality of published literature in order to answer a very specific question. By contrast, a systematic mapping review characterizes the literature and catalogs it according to a criteria or framework or model. In this study, the published literature on tele-neurorehabilitation will be described and categorized using the TAM3 framework. A systematic mapping review process is particularly useful when the topic area is broad and the quality and range of studies is diverse (37–39). This approach can provide information about knowledge gaps and therefore direct future research, including systematic reviews.

The methods applied to a systematic mapping review process are as follows: (1) literature search, (2) literature selection, and (3) literature mapping to the TAM3.

Literature Search

Databases relevant to the health sciences were searched including CINAHL (EBSCO), PsycINFO (EBSCO), PubMed (National Center for Biotechnology Information), and SCOPUS. Search terms were telerehabilitation or tele-rehabilitation or telehealth or remote rehabilitation AND stroke or cerebrovascular accident or CVA AND home or remote. Limitations included English-language, adult population and peer-reviewed papers. The search date was for studies published from 2000 to July 2020.

Literature Selection

The aim of this study was to determine if the existing literature on tele-neurorehabilitation could be mapped using the TAM3, with a specific focus on the user experience. Therefore, studies which included any information on patient or therapist experience of tele-neurorehabilitation, were a particular target. Following removal of protocols, center-based interventions and systematic reviews, a total of 22 studies were identified. **Table 1** presents data extracted from the studies including aims, population and outcomes. The studies included pre/post-studies, evaluation of devices, and qualitative exploration of user experience with tele-neurorehabilitation. Participants were stroke survivors in acute, sub-acute or chronic phases of recovery and varied in their impairments. Consequently, the tele-neurorehabilitation interventions included sit-to-stand practice, communication therapies, psychosocial interventions and activities of daily living practice. The type of ICT used also varied widely from telephones to apps with associated sensor data.

Literature Mapping to TAM3

All 22 studies were readily able to be mapped on to the TAM3 and revealed patterns in relation to the barriers and facilitators for tele-neurorehabilitation. **Figure 1** displays the findings using the TAM3 model which is expanded on in the following sections.

RESULTS

Tele-Neurorehabilitation and Perceived Usefulness

Do Stroke Survivors and Clinicians Perceive That Tele-Neurorehabilitation Will Be Beneficial?

The majority of studies found that tele-neurorehabilitation interventions were not inferior to conventional center-based models of care (41, 42, 46, 47, 50, 54–56, 60). Patients and carers/family reported subjective improvements in communication, gait, activities of daily living, and motivation. Only one study found that patients preferred a conventional home exercise program over tele-neurorehabilitation due to the perception that the tele-neurorehabilitation was too complex (59). None of the studies explored therapist perceptions of the usefulness of tele-neurorehabilitation, particularly in comparison to conventional models of center-based neurorehabilitation.

Tele-Neurorehabilitation and Perceived Ease of Use

Do Stroke Survivors and Clinicians Perceive That Tele-Neurorehabilitation Is Easy to Use?

A number of studies found that participants enjoyed gaming technology associated with some of the tele-neurorehabilitation interventions and found them easy to use, engaging and motivating (41, 43, 47, 48, 52, 54). Experiences with both hardware and software had a marked effect on the user perception of tele-neurorehabilitation. For example, hands-free systems were perceived as easier to use (60) than those that required the participant to don/doff splints, sensors, and other similar hardware (40–42, 45, 56, 57).

TABLE 1 | Data extraction for studies included in the mapping review.

Author (date, country)	Study design sample	Study aim	Intervention	Outcomes measured	Results
Burdea et al. (40)	Pre/post Stroke survivors and their caregivers ($n = 8 + 8$)	To evaluate the feasibility of a tele-neurorehabilitation system developed for the study	4-weeks (20 sessions) participating in serious gaming with Grasp game controller	Motor function and impairment Emotion and cognition Survey of user experience	High rate of compliance Improvement in mood and cognition Participants had an overall positive attitude to the system Both carers and participants scored technical problems as the lowest
Chen et al. (41)	Qualitative Stroke survivors $N = 13$ participants	To investigate patient perceived benefits of and barriers to using a telerehabilitation system at home	6-weeks using a home-based telerehabilitation system with serious gaming 18 sessions supervised 18 sessions unsupervised	Semi-structured interviews exploring attitudes, motivation and usage	Perceived improvement in physical abilities, psycho-social health and well-being Participants intended to continue to use the system provided improvements in games and progress feedback were made
Cherry et al. (42)	Qualitative Stroke survivors $N = 10$	To determine participants' general impressions about the benefits and barriers of using robotic therapy devices for in-home rehabilitation	2-h daily robotic assisted therapy for a maximum period of 3-months	Direct observation In-depth semi structured interviews exploring the user experience	Benefits included increased mobility, sense of control over therapy and outlet for stress and tension Barriers were donning the hardware (arm device) and technical difficulties
Cronce et al. (43)	Case Report Stroke survivor $N = 1$	To evaluate the feasibility of a virtual rehabilitation system developed for the study	7×30-min training sessions using the VR system and serious gaming	Questionnaire exploring system use	Easy to use system that was highly engaging and motivating
Deng et al. (44)	Pilot RCT Stroke survivors Experimental $N = 8$ Control $N = 8$	To explore feasibility of using telerehabilitation to improve ankle dorsiflexion and to compare complex vs. simple movements of the ankle	4-weeks of telerehabilitation using a computerized system	Gait 10-meter walk test fMRI Participant feedback	Improved ankle dorsiflexion Difficulties donning hardware but overall
Deutsch et al. (45)	Case Report Stroke Survivor Clinician ($N = 1 + 1$)	To describe the outcomes of using motor imagery via a telerehabilitation platform	3×45–60-min sessions over 4-weeks using motor imagery delivered in the home with telerehabilitation	Imagery ability Motor behavior Fugl-Meyer Timed up and Go Questionnaire on system usability	Improvement in gait and balance Both patient and clinician found the system useful Lowest score for functions and capabilities of the system
Dodakian et al. (46)	Pre/Post Stroke survivors $N = 12$	To assess feasibility and motor gains of a telerehabilitation system developed for the study	28-days of home-based telerehabilitation delivered in $2 \times$ 14-day blocks System consisted of specialized computer, table and set up for serious gaming	Vital signs Arm motor function Mood QoL Survey of patient experience with the technology	Improvement in arm motor function compliance and satisfaction with the system Improved stroke prevention knowledge No correlation between computer literacy and outcomes
Ellington et al. (47)	Pre/Post Stroke survivors $N = 14$	To investigate the behavioral intention to use a virtual system for practicing instrumental activities of daily living	4×1 h sessions using affected upper limb to practice two virtual activities e.g., meal preparation	Questionnaire based on the TAM Semi-structured interview	Positive attitude and intention to use technology Relationship between perceived usefulness and intention to use

(Continued)

TABLE 1 | Continued

Author (date, country)	Study design sample	Study aim	Intervention	Outcomes measured	Results
Flynn et al. (48)	Case report Stroke survivor *N* = 1	To explore the use of a low-cost virtual reality device	20 × 1-h sessions using a low-cost virtual reality device with associated serious gaming	Fugl-Meyer Timed up and go Daily logs of system use In-depth interview	Improvement in motor function, mood, mobility and gait Reported the system was motivating
Kurland et al. (49)	Pre/Post Stroke survivors *N* = 21	To determine if a table-based home practice program could enable maintenance of treatment gains in post-stroke aphasia	6-month home practice program with weekly teletherapy sessions	% accuracy on naming Boston naming test	Greater number of training sessions with the technology resulted in fewer gains in naming accuracy
Lai et al. (50)	Pre/Post Stroke survivors *N* = 21	To evaluate the feasibility of using videoconferencing for community-based stroke rehabilitation	8-week intervention delivered at a community center for seniors via videoconferencing. Included education modules, exercise and psychosocial support	Balance Self esteem Stroke Knowledge Mood ADL Focus group discussions exploring satisfaction	Improvements in balance, self-esteem, stroke knowledge and quality of life. 67% rated clinical effectiveness of the system as good
Langan et al. (51)	Cross-sectional study Therapists *N* = 107	To examine the extent to which physical and occupational therapists use technology in clinical stroke rehabilitation programs	N/A	Survey measuring use of technology	Poor use of technology even when available
Piron et al. (52)	Pilot study Stroke survivors *N* = 10	To compare degree of satisfaction of patients using virtual reality therapy programmed at home with those using the same system in a hospital setting	1-h of rehabilitation daily for 1 month involving virtual tasks practiced in a VR system	Fugl-Meyer scale Questionnaire measuring degree of satisfaction	High compliance Tele-neurorehabilitation group had a lower score for therapist explanation of the treatment, higher outcome for UL motor
Rogerson et al. (53)	Mixed-methods evaluation Chronic stroke survivors *N* = 19	To assess the feasibility and acceptability of a smart home system that monitors users' activity	Installation of a system and participant education on how to use it	Interview on user experience of the system	The technology gave peace of mind Engagement with the system was variable
Seo et al. (54)	Pre/Post Chronic stroke survivors *N* = 10	To assess usability of a virtual reality rehabilitation system	Not described	Survey of user experience	Preference for easy to use games
Simpson et al. (55)	Pre/Post Stroke survivors *N* = 8	To investigate the feasibility of a phone-monitored home exercise program for the upper limb following stroke	8-week home exercise program with weekly telephone contact with therapist	Chedoke arm and hand inventory Motor activity log Grip strength Occupational performance Feasibility outcomes	Did not achieve exercise adherence or goal rates Motor improvement maintained at 3 and 6 month follow up
Simpson et al. (56)	Pre/Post Stroke survivors *N* = 10	To determine whether telerehabilitation is feasible in monitoring adherence and progressing functional exercises at home	4-weeks of telerehabilitation using an app with serious gaming and sensor system to monitor movements	Short physical performance battery (SPPB) Timed sit-to-stand test Satisfaction questionnaire	High compliance with the program High ratings for system usability, enjoyment and perceived benefits Improvement in SPPB
Standen et al. (57)	Prospective cohort study Stroke survivors *N* = 17	To investigate patient use of a low-cost virtual reality system	Equipment left in patient homes for 8-weeks with advice to use 3 times per day for maximum 20 min	Duration, frequency and intensity of use	Lack of familiarity with technology impacted use

(Continued)

TABLE 1 | Continued

Author (date, country)	Study design sample	Study aim	Intervention	Outcomes measured	Results
Threapleton et al. (58)	Cross-sectional study Acute stroke survivors ($N = 4$) Chronic stroke survivors ($N = 8$) Occupational therapists ($N = 13$)	To explore the value of virtual reality in preparing patients for discharge following stroke	Demonstration of a virtual home application prior to the interview	Semi structured interviews	Occupational therapists felt the system had the potential to educate and engage the patients in preparing for discharge home but may not be suitable for all patients Stroke survivors felt the system was not representative of their own homes
Triandafilou et al. (59)	Pre/Post Stroke survivors $N = 15$	To evaluate a virtual environment system developed for the trial and compare to an existing virtual reality system and a home exercise program (HEP)	1-week participation in each of the three interventions (total of 3-weeks)	Arm displacement Survey to measure participation and satisfaction	Low satisfaction with time spent in training for the VR system Preference for HEP over the other two systems
Warland et al. (60)	Pre/Post Chronic stroke $N = 12$	To establish feasibility, acceptability and preliminary efficacy of an adapted version of a commercially available, virtual-reality gaming system for upper-limb rehabilitation	9×40-min exercise sessions utilizing the system for 30 days per week over 3-weeks	Semi structured interview to explore feasibility and acceptability Fugl-Meyer Assessment Action research arm test Motor activity log Participation	High level of enjoyment Improvement in all motor and function outcomes
Woolf et al. (61)	Quasi-randomized controlled feasibility study Chronic stroke survivors with aphasia $N = 21$	To test the feasibility of a randomized controlled trial comparing face to face and remotely delivered word finding therapy for people with aphasia	8×1 h therapy delivered using videoconferencing technology compared to face to face therapy and an attention control condition	Word retrieval Recruitment and attrition rates Participant observation and interviews Treatment fidelity	Treatment fidelity was high Compliance and satisfaction with the intervention were good Picture naming improved but not naming in conversation

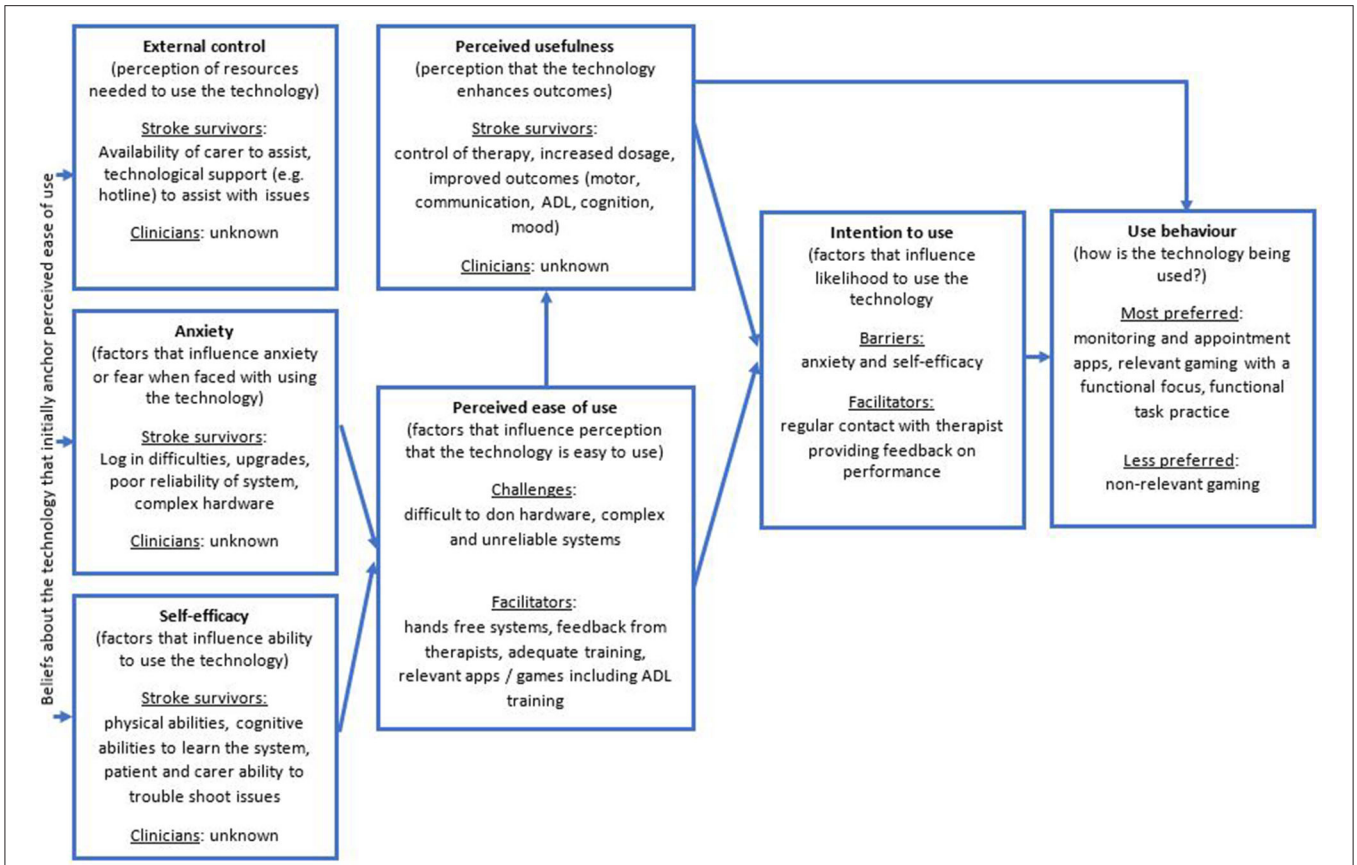

FIGURE 1 | Result of mapping the 22 studies to the variables of the TAM3 (31).

Low self-efficacy related to the tele-neurorehabilitation system used was a frequently reported problem that affected perception of ease of use, compliance, and subsequent intention to continue using the system in the future (57, 60). Conversely, prior experience with relevant technology, such as computers, correlated to improved compliance and perceptions of ease of use (46, 53).

Anxiety and frustration with tele-neurorehabilitation was apparent when more complex ICT and hardware was used (42, 44, 46). Unreliable internet bandwidth, and technical issues which were not easily resolved further contributed to anxiety and perceptions of ease of use (46). Studies where the ICT was familiar (e.g., telephones) and consisted of easy to understand tasks (e.g., sit-to-stand practice) appeared to reduce anxiety secondary to the perception that they were easier to use (47, 56).

Increased exposure and practice with tele-neurorehabilitation systems improved compliance and reduced anxiety related to low confidence and proficiency with technology (46, 48, 49, 59). However, the amount of experience necessary to reduce technology-related anxiety remains unclear with studies reporting variable amounts of time spent on training participants and therapists. Conversely, one study found there was a correlation between number of training sessions to achieve proficiency in using the technology and poorer outcomes, indicating that the technology may not be suitable for all disorders or patients (49).

The most commonly reported external variable necessary to support engagement in tele-neurorehabilitation was the presence of a carer/family member (44, 46, 61, 62). This was the case irrespective of the nature of intervention being delivered or the type of ICT being used.

Tele-Neurorehabilitation and Behavioral Intentions

Are Stroke Survivors and Clinicians Motivated or Willing to Exert the Effort to Engage in Tele-Neurorehabilitation?

A number of studies found that participants reported an intention to continuing engaging in tele-neurorehabilitation, with some provisos, including a request for easier and more reliable technology and access to their performance results (40, 41, 47, 52, 53).

Tele-Neurorehabilitation and Use Behavior

How Are Stroke Survivors and Clinicians Using Tele-Neurorehabilitation?

Tele-neurorehabilitation with a focus on relevant, easy to use components was rated more highly by participants than complex

systems with multiple componentry (46, 53). For example, appointment reminder systems, monitoring apps and ADL focused gaming was selected more often than motor-based gaming. Participants also preferred tele-neurorehabilitation systems where the therapist could observe and provide feedback and encouragement via a videoconferencing or other interactive system (41, 45, 54, 56).

DISCUSSION

It is anticipated that the demand for neurorehabilitation will continue to grow due to an aging population and high incidence rates of diseases such as stroke. Rehabilitation resources in both developing and developed countries are limited and the need to find alternative yet effective and efficient models is imperative. Tele-neurorehabilitation has great potential to increase accessibility to rehabilitation for individuals with neurological impairments. However, consideration must be given for both human and ICT factors that can hinder or facilitate adoption of tele-neurorehabilitation.

A review of the published evidence on tele-neurorehabilitation through the lens of TAM3 reveals that perception of ease of use is influenced by the user's belief that they have the requisite skills and ability to use the technology (computer self-efficacy) and the degree of apprehension or fear they experience when faced with learning to use the technology (computer anxiety). Easy to use ICT and adequate experience using the technology assists the user to adjust their beliefs about computer self-efficacy and reduces computer anxiety (46, 63). Some studies found that patients were open to and excited about tele-neurorehabilitation but experienced numerous technological malfunctions which increased computer anxiety and reduced perceived enjoyment (64). Nearly all studies found that carers were critical to ensure that patients were able to overcome barriers related to system set-up, thus reducing computer anxiety (63).

There is little to no evidence on the feasibility of tele-neurorehabilitation for the "typical" stroke survivor who is likely to have cognitive impairment. Published studies have found that patients with cognitive impairment can benefit from computer training programs, suggesting that at least some of these patients may have computer self-efficacy and be appropriate for a tele-neurorehabilitation intervention. There is little to no evidence on how much experience or practice and training with a system is needed for the stroke survivor to become a confident user. Understanding the type and frequency of training necessary to establish and maintain computer self-efficacy would contribute to a more informed implementation and sustainable adoption of tele-neurorehabilitation.

Although gains have been made in design of ICT to potentially enhance tele-neurorehabilitation, barriers to adoption that were identified more than 20 years ago remain apparent today (65). These barriers are relevant for both patients and prescribing clinicians and include poor computer self-efficacy, high computer anxiety, low perception of usefulness and a belief that the technology is not user-friendly (65, 66). If we are to realize the full potential of tele-neurorehabilitation, it is of critical importance that we approach the topic using a validated and well-tested theoretical framework to guide and evaluate implementation. This would make a significant contribution to the evidence-base on tele-neurorehabilitation.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

MK and MG conceived the ideas presented. MK completed the initial draft of the manuscript which was reviewed and edited by MG resulting in the final manuscript. All authors contributed to the article and approved the submitted version.

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Remote Assessment of Post-Stroke Elbow Function Using Internet-Based Telerobotics: A Proof-of-Concept Study

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Purpose: Upper limb hemiparesis is the most common impairment in stroke survivors, and adequate assessment is crucial for setting the rehabilitation strategy and monitoring the effect of treatment. However, adequate timely assessments are difficult due to the limited accessibility to clinics for stroke survivors. We designed this study to investigate whether teleassessments for motor impairments of the spastic elbow (i.e., passive range of motion (PROM), muscle strength, and spasticity) are feasible in stroke survivors.

Methods: To implement a telerobotic system for remote assessment with physical interaction, we constructed a system with a master robot interacting with a doctor (assessor) and a slave robot interacting with the elbow of a subject with stroke. The master robot is operated by the doctor, where the torque and the speed are transferred to the slave robot via the Internet, and the reaction of the patient's elbow to the slave robot's movement is measured with a torque sensor, then finally transferred back to the master robot. An intercontinental remote assessment, which is considered one of the worst possible scenarios, was used as a clinical test to strictly check the feasibility. For the clinical tests, the examiner for the teleassessment was located at a lab in the National Institutes of Health (NIH, Bethesda, MD, USA) while the stroke patients were located at Seoul National University Bundang Hospital (Bundang, Kyeonggido, South Korea).

Results: In total, 12 stroke patients' elbows (age range, 28–74; M:F = 6:6) were tested. For the PROM, the absolute difference between two assessments (in-person vs. remote) was 5.98 ± 3.51° on average (range, 0–11.2). The agreements for the strength and the spasticity of elbow flexor between in-person and remote assessments were substantial ($k = 0.643$) and fair ($k = 0.308$), respectively. No adverse events were observed during or immediately after the telerobotic assessment.

Conclusions: Internet-based telerobotic remote assessment for motor impairment of spastic elbow in stroke using our system is feasible even in the worst setting, with too long of a distance and a delayed communication network.

Keywords: telemedicine, telerehabilitation, telerobotics, bilateral haptic feedback, remote assessment, stroke, internet

INTRODUCTION

The rapid growth of information and communication technology (ICT) has brought people closer to each other. In healthcare, ICT enables telehealth, which is the remote delivery of health-related services and information (1). Telerehabilitation, a subcomponent of telehealth, is the clinical application of telecommunication technology to provide interventions as well as assessments to patients undergoing rehabilitation in remote locations (2, 3). It can be used to provide cost-effective care and specialized rehabilitation service to patients living far from a rehabilitation center due to the reduced travel time and cost between health centers and the patient's home, as well as direct linkage between the rehabilitation specialist and patient (4). Telerehabilitation will become more important as an increasing number of patients with disabilities require a rehabilitation service in the face of the increasingly aging population as well as the limited accessibility to rehabilitation services due to transportation problems or limited medical staff availability, particularly in rural areas (2). In addition, the current pandemic crisis is revealing the importance of telerehabilitation, which enables the delivery of rehabilitation services without the risk of virus exposure.

Telerehabilitation services can be classified into the two categories of intervention and assessment, both of which are essential. Most studies investigating assessment have attempted to implement video conferencing systems between clinicians in a health center and patients in a remote location such as their home (5). However, these attempts are still far from in-person assessments; for example, all of the assessments lack any physical interaction between clinician and patient (6, 7). Since one of the major targets of rehabilitation is to improve the patient's physical impairments, i.e., plegia, weakness, and spasticity, a clinician needs to assess the impairments by conducting in-person physical exams that involve physical interaction. Without such interaction, the clinician's assessment ability is limited, and the assessment accuracy is degraded (3, 6, 8).

In stroke rehabilitation, comprehensive assessment is essential for proper treatment, quality control, and evaluating training outcomes (9). With the recent advancements in ICT, pilot studies on the telerehabilitation assessment of stroke survivors have been increasing (6). The validity and the reliability of telerehabilitation assessment have mainly been reported in terms of the areas of pain, swelling, the range of motion of joints, muscle strength, balance, gait, posture, special orthopedic testing, and neurodynamic testing, mostly using video conference systems (8, 10–13). The studies mentioned above have two main limitations: The first is that ROM and muscle strength show high validity, whereas posture, special orthopedic testing, and neurodynamic testing have low to moderate validity. Second, video conference systems do not allow for physical interaction between the patient and the evaluator in a remote area (8). Allowing for physical interaction in addition to the video conferencing in telerehabilitation assessment would increase the validity of the assessment. For example, spasticity is a symptom of neurological impairment which is prevalent in patients with stroke, and it plays a very important role in the restoration of function (14). In the recovery of upper limb function after stroke, it is important to accurately evaluate spasticity, particularly elbow spasticity. This is important for evaluating the effectiveness of physical therapy, deciding whether to treat spasticity with Botox injection and medication, and evaluating the effectiveness after treatment (14, 15). However, few studies have evaluated spasticity in telerehabilitation assessment, and the validity of neurodynamic tests is reported to be relatively low (10, 11, 13, 16).

To implement physical interaction between remote locations, a remarkable pilot study for assessing spastic elbow was reported (17). Telerobotics (or bilateral teleoperation) is a concept in the field of robotics which aims to extend the operator's ability (manipulation as well as sensation) to remote areas (18). Since the aim was exactly matched to the required physical interaction for remote assessment, that study attempted to adopt telerobotics technology to provide this interaction. Although the result showed potential usage, it still had several limitations: (1) providing distorted physical interaction due to intuitive robotic devices and control architecture and (2) failure to evaluate the remote assessment due to a limited clinical test with an ideal setup, a small population, and no comparison based on clinical instruments (6). Another study developed a telerobotic device for the remote assessment of hands, but the device was not evaluated in a clinical setup (19).

Hence, the aim of this paper is twofold: improving physical interaction for remote assessment and evaluating that remote assessment. For the former, we developed a novel haptic device to minimize friction that would result in a clinician's inaccurate feeling of the subject's muscle tone, and we applied a control architecture to guarantee stable implementation of physical interaction with time delay that exists in telecommunication, such as the Internet. For the latter, we conducted the clinical test with a challenging setup: an intercontinental Internet-based remote assessment between USA and South Korea. Since time delay is a critical issue in real-time remote assessment, we test this setup as it is the most difficult situation for real-time bilateral physical interaction. Twelve stroke patients with spasticity participated in the clinical test, and typical clinical instruments for the assessment, such as the medical research council scale (MRC) and the modified Ashworth scale (MAS),

were used for the comparison between the in-person assessment and the proposed remote assessment.

MATERIALS AND METHODS

Subjects

Twelve stroke patients (six men and six women, 52.6 ± 16.6 years old) with impaired elbows participated in the study (**Table 1**). They gave written informed consent approved by the Institutional Review Board at SNU Bundang Hospital (IRB approval No.: E1101/058-001).

Instrumentation

Telerobotic System for Remote Assessment

In robotics, telerobotic systems have often been used to enable physical interaction between the operator and the environment, with the target object in a remote area. As illustrated in **Figure 1**, such a system consists of a master robot (haptic device) that interacts with the operator, a slave robot that interacts with the environment, telecommunication between the master and the slave, and a control architecture to implement the physical interaction. For the remote elbow assessment, the operator is the clinician who assesses the patient's affected elbow, while the elbow constitutes the environment (**Figure 1**).

Patients with stroke typically develop several impairments at their affected elbow, such as reduced range of motion (ROM), muscle weakness, and spasticity. Hence, we use the following three tests as the target tasks of the remote assessment: 1) passive ROM test, 2) muscle strength test, and 3) spasticity test. Note that those tests were also used in a previous study on the remote assessment (17).

Telerobotic Devices

As mentioned previously, the telerobotic system includes two robotic devices, the master and the slave. During the remote assessment, the clinician must manipulate the master device to move the patient's affected elbow and feel the muscle tone caused by the movement in the elbow. Thus, for accurate assessment, it is crucial for the master device to recreate the resistance (muscle tone) of the affected elbow that the clinician would have felt during an in-person assessment.

In an attempt to reduce the friction, we developed a master device that adopts a cable-driven mechanism, as shown in **Figure 2**. Through this mechanism, the force/torque generated by a brushless DC motor (Barrett Technology Inc., Cambridge MA) is transmitted to the mannequin arm which mimics the patients' forearm. Since the mechanism utilizes frictionless rolling contact of two adjacent pulleys driven by two steel cables which are pre-tensioned but do not stretch, it can implement a negligible level of friction. To verify the amount of the friction that would be felt by the clinician, we conducted an experiment in which the friction caused by the mechanism was measured using a torque sensor (TRT-200, Transducer Technique Inc., Temecula CA) while the clinician manipulated the mannequin arm with zero motor command. **Figure 3** shows that the maximum friction torque was <0.2 Nm, which is small enough to not distort the feel of the resistance due to the affected elbow.

In addition, for the remote assessment, a slave device is needed to move the elbow by following the command generated by the master and to measure the resistance caused by the affected elbow. We developed an exoskeleton-type slave robot, shown in **Figure 4**. It contains a brushed DC motor (RE-50, Maxon Motor, Switzerland) to mimic the clinician's movement and a torque sensor (TRT-200, Transducer Technique Inc., Temecula CA) to sense resistance during that movement. The braces in the slave robot were designed to easily attach to and detach from the patient's elbow and to make the patient comfortable while the robot and the patient's forearms move together. The slave robot was equipped with an emergency stop, and the clinician was ready to press the button whenever necessary to ensure safety.

Control Architecture

Clinicians need physical interaction with the patients for remote assessment. This can be implemented using a bilateral control architecture that virtually achieves transparent interaction with a certain environment through a telerobotic setup (20). Over the last decade, many control architectures have been reported to provide more transparent interaction, but they have not been able to overcome the well-known conflict between transparency and stability (21, 22); as illustrated in **Figure 1**, time delay due to communication is unavoidable in a telerobotic system, and it is not easy to achieve stable and transparent interaction under time delay. However, stability is also essential for remote assessment because instability can lead to patients' injuries.

A novel control architecture, a two-channel control architecture, has been proposed to overcome this conflict. Since the control architecture provides stable and optimized transparent interaction under a feasible time delay (about up to 500 ms) (23), it can resolve this conflict. Hence, in this paper, we use a two-channel F-P control architecture to implement the physical interaction using master and slave robots. As illustrated in **Figure 5**, in this architecture, the force of the master followed the transmitted force measured from the slave, and the slave was commanded to follow the position of the master (23). For simplicity, the force controller of the master was not a closed-loop feedback controller but an open-loop

TABLE 1 | Summary of participants ($N = 12$).

	Sex	Age (year)	Time since stroke (month)	Affected side
PT01	M	40	1	R
PT02	M	57	3	R
PT03	F	74	7	R
PT04	F	35	29	L
PT05	M	59	54	L
PT06	M	46	30	R
PT07	F	28	48	L
PT08	M	28	37	L
PT09	F	73	27	R
PT10	M	65	92	R
PT11	F	62	49	L
PT12	F	64	27	L

FIGURE 1 | Telerobotic remote assessment.

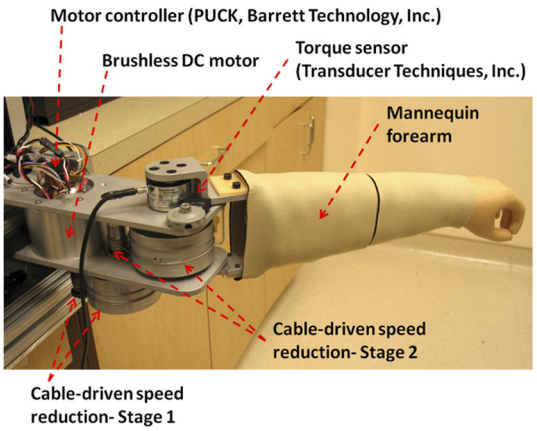

FIGURE 2 | The master robot (clinician site in US).

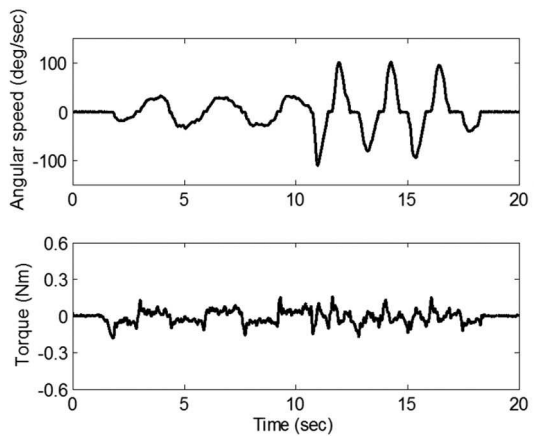

FIGURE 3 | The level of friction due to the cable-driven mechanism in the master device.

feedforward controller. Since the dynamics of the master device can be accurately estimated due to its low friction, the performance of force tracking with the feedforward controller was sufficient to provide appropriate resistance force/torque for the clinician.

To enable communication between the master and the slave, we used the public intercontinental Internet line. The transfer of the current position/force information of the master/slave was implemented with custom-built software using the UDP protocol, which contains checksum to avoid packet corruption/loss for safety. In addition, the Google Hangouts™ application (Google, CA, USA) was used for the video conference between the clinician and the patient.

Protocol

As mentioned previously, time delay is a critical burden in remote assessment. Therefore, the clinical test for evaluating the assessment was conducted with the worst case we could test: intercontinental Internet-based remote assessment between South Korea and the USA. In this assessment, the master and the slave robots were, respectively, located at the Robotics Laboratory in the National Institutes of Health (Bethesda, MD, USA) and at the SNU Bundang Hospital (Bundang, South Korea). Due to the heavy load and the long distance of the intercontinental Internet line, there was a remarkable time delay of up to 500 ms.

First, a clinician who has 5 years of experience in the hospital examined the subject through passive ROM, muscle strength, and spasticity testing. The clinician used a goniometer to measure the ROM of the subject's affected elbow. The muscle strength was rated according to the medical research council (MRC) score. One inspector measures the ROM and the MRC twice each and used the average of the values. The spasticity of each flexor/extensor was assessed using the modified Ashworth scale (MAS). When measuring the MAS, we conducted the assessment tasks three to five times using the standard protocol (24). The clinician grasped patient's forearm and upper arm and stretched the elbow with a speed of 1 s for full elbow extension. The multiple trials started in a random manner so that the patients could not expect the stretch. The clinician gave MAS score based on the observation of the multiple trials.

After the in-person assessment, the subject was asked to put the slave robot on their affected elbow. The shoulder height of the subject was determined to a natural posture where the shoulder girdle is not elevated or depressed. The elbow joint axis was aligned with the slave robot axis by moving the forearm while wearing the slave robot and adjust the elbow joint position that does not make any slide motion with the arm and brace part of the slave robot. After that, the subject's neutral joint position was determined manually by the clinician using a goniometer and the angle of the master device was synchronized with the slave device at the neutral joint position to eliminate the angle difference. Next, the following three remote assessment tasks were carried out by a clinical staff who has 6 years of experience in spasticity, muscle strength, and range of motion assessment, as shown in **Figure 6**.

1) Passive ROM test: At the beginning of the assessment session, the clinician slowly moved the mannequin arm at the master device. This commanded the slave device, through the Internet, to move the subject's elbow in the same way, and the resistance torque at the subject's elbow was recreated in the master device to provide real-time haptic feeling of the subject's elbow joint to the clinician. Due to this haptic feedback, the clinician could remotely detect the position limits in both elbow flexion and extension under controlled peak resistance torque. This test was taken twice, and the ROM was determined based on the minimum and maximum angles measured during the test (**Figure 6A**).
2) Muscle strength test: Using the video conferencing tool, the clinician asked the subject to flex/extend his or her elbow while the clinician remotely held the elbow at a selected position. The slave device simply held the subject's elbow according to the position of the master device, and the subject repeated three flexion and extension motion in isometric conditions with 15 s rest between each trial. The measured torque generated by the subject was sent to the master device and the clinician felt the torque generated by the subject during the test, then rated the MRC score (**Figure 6B**).
3) Spasticity test: Spasticity was evaluated remotely by moving the subject's elbow through the ROM determined above. The resulting "muscle tone" was felt by the clinician remotely, which allowed the clinician to make a determination about the MAS score, a measure of the spasticity. The passive movement was done three to five times in both flexion and extension as well as at several velocities to determine MAS score clearly, simulating those in clinical examinations (**Figure 6C**).

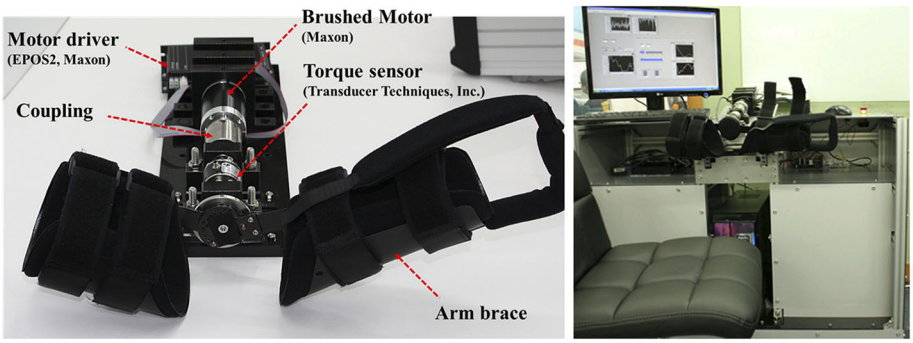

FIGURE 4 | The slave robot (patient site at SNUBH, South Korea).

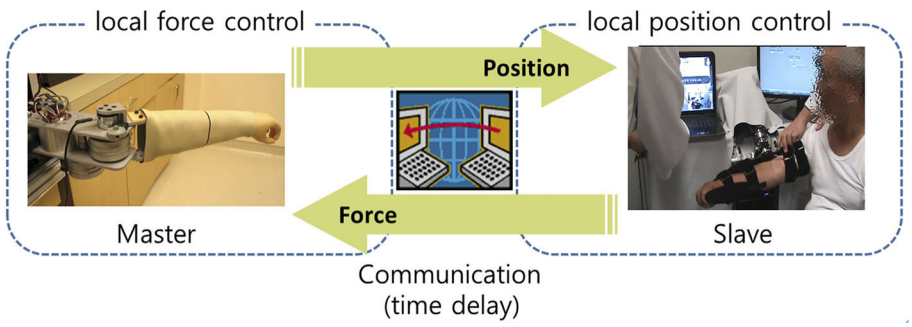

FIGURE 5 | Two-channel F-P control architecture.

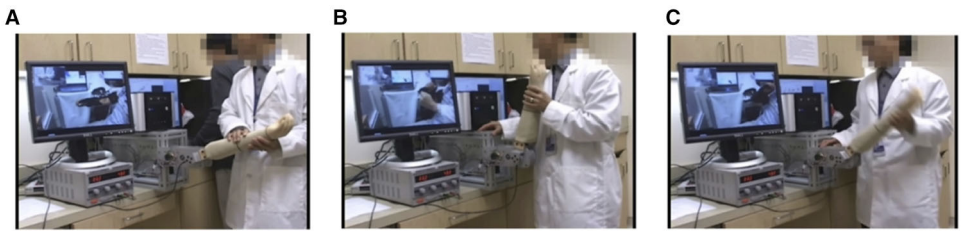

FIGURE 6 | Three remote assessment tasks. **(A)** Passive ROM. **(B)** Muscle strength. **(C)** Spasticity.

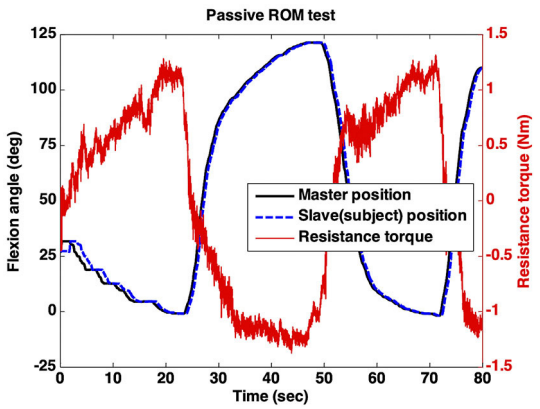

FIGURE 7 | Remote passive ROM test.

TABLE 2 | Comparison of outcomes (PROM, MRC, and MAS) between in-person and remote assessments.

	Passive ROM (deg)		MRC scale		MAS	
	In-person	Remote	In-person	Remote	In-person	Remote
PT01	130	140.4	5	5	0	0
PT02	130	131.8	3	3	1+	1+
PT03	134	125.8	4	4	0	0
PT04	130	131.5	5	5	2	0
PT05	135	130.1	4	4	2	1
PT06	120	131.2	5	5	1+	0
PT07	140	140.0	4	3	1	0
PT08	141	135.7	4	4	2	2
PT09	111	118.7	3	2	2	2
PT10	130	121.5	5	5	1	2
PT11	128	122.0	3	3	2	2
PT12	134	127.7	4	3	1+	2

Data Analysis

To evaluate the proposed remote assessment, the clinical outcomes of the assessment were compared with those of in-person assessment. The ROM error, defined as the difference of ROM between in-person and remote conditions, was calculated to evaluate the passive ROM test. For muscle strength and spasticity, the agreement between in-person and remote assessments was evaluated using Cohen's kappa statistics.

RESULTS

Passive ROM Test

Figure 7 shows a representative passive ROM test that was remotely conducted using the telerobotic device. As shown in the figure, the slave position (blue line) followed the master position (black line) with a time delay. For instance (PT11), as shown in **Figure 7**, the clinician started to move the master at the initial position and stopped at a near-zero flexion angle (0.5°) due to increased resistance torque. As a result, the position limit of elbow extension was determined to be 0.5°. Next, the master was flexed by the clinician again while significant resistance torque appeared. Therefore, the position limit of elbow flexion was determined to be the end position (122.5°) measured by the encoder attached to the master. Those two position limits result in an outcome of remote assessment indicating 122° passive ROM of the subject's affected elbow.

The passive ROMs obtained by remote assessment were compared with those obtained by in-person assessment, and the comparison is presented in **Table 2**. The absolute differences between the two ROMs were <6° on average (5.98 ± 3.51°).

Muscle Strength Test

In this test, the subjects did their best to maintain the position (flexion angle) shown in **Figure 6B** against the force applied remotely by the clinician. **Figure 8** shows the data of two representative subjects in the proposed remote assessment setup. One subject with good muscle strength (MRC 5) was able to generate large resistance torque to compensate for the force that was applied by the clinician, as displayed in **Figure 8A**. By contrast, the other subject (MRC 3) achieved negligible resistance torque against the clinician's movement (**Figure 8B**).

The MRC scales rated by in-person assessment and remote assessment are summarized in **Table 2**. The results show substantial agreement between the two MRC scales ($k = 0.643$).

Spasticity Test

In this test, the clinician manipulated the master device quickly, as displayed in **Figure 6C**. This fast movement resulted in a rapid increase in the resistance torque caused by the subject's impaired elbow. MAS 1 indicates a small but rapid increase in the resistance torque. Since a large and rapid increase appeared and remained at almost the total ROM of the elbow, MAS was determined to be 2 (**Figure 9**).

As summarized in **Table 2**, the MAS rated by in-person and remote assessments only had fair agreement ($k = 0.308$). The clinician rated the MAS according to the size of the increase and the start/end positions of the increased torque. As shown in **Figure 9**, the clinician most felt the increase at the end of ROM of the elbow due to the time delay. Hence, the start/end positions of the increased torque were not clear.

DISCUSSION

This paper implemented and tested remote real-time physical assessment. Considering that physical assessment involves haptic feel between the examiner and examinee, it would be more realistic to implement haptic interaction at remote locations through the use of telerobotic control technology. Using a teleoperated robot in the rehabilitation field may help cost-effectively solve the accessibility issues involved when a patient and a rehabilitation specialist are not able to meet face to face. For example, rehabilitation service access may be limited in patients living in areas far from rehabilitation facilities (25). In this situation, simple instructions and training given to the person who will manage the slave robot may be sufficient to provide

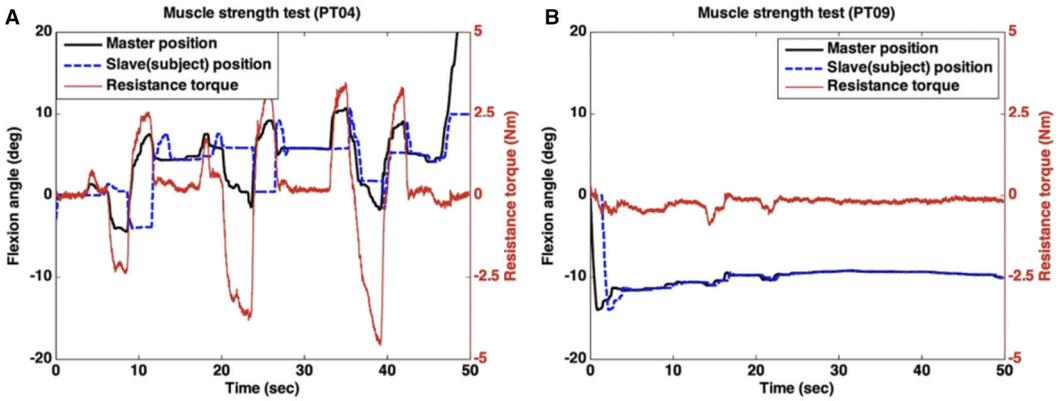

FIGURE 8 | Remote muscle strength test. **(A)** MRC3 case, **(B)** MRC5 case.

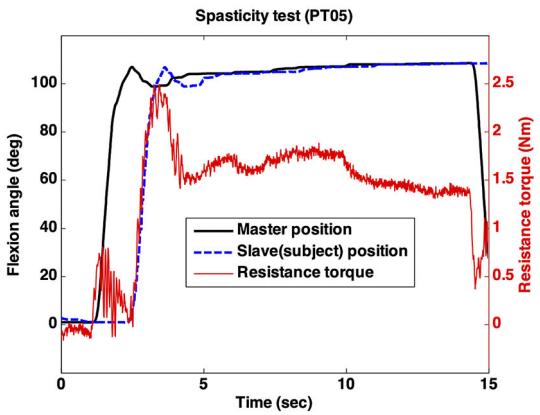

FIGURE 9 | Remote spasticity test.

telerehabilitation operated by a remotely located rehabilitation specialist, without travel. This clinical scenario is also relevant to developing countries that have limited rehabilitation human resources (26) and isolated conditions in some regions and medical or nursing facilities due to outbreaks of communicable diseases. In situations like the recent COVID-19 outbreak, this system may be helpful for protecting the therapist in intrahospital rehabilitation services.

Although the 1 DoF robotic system in this study is limited to use in arm rehabilitation after central nervous system injury, this concept of a teleoperated robot with haptic feeling can also be applied to a multidimensional rehabilitation robot, which may be useful for telerehabilitation beyond teleassessments (27). Our system is also promising as it may provide education to potential rehabilitation therapists in developing countries. Knowledge transfer is possible through lectures using video conferencing, but hands-on education is necessary for rehabilitation training. Therefore, education with a teleoperating haptic robotic system provided by an experienced therapist in developed countries may be more effective than online lectures alone. This tele-education may also be more cost-effective than onsite education with a visit by a trained therapist, considering cost for travel, accommodation, and travel time (indirect cost).

Due to the control architecture and low friction of the master robot, the performance of a real-time teleassessment system mainly relies on the time delay between the examiner and examinee. According to the teleoperation control theory (21), the time delay degrades the quality of the haptic feel and the stability of the robotic systems. We have tested our experimental setup under a maximum time delay of 500 ms, and the performances of the passive ROM and the muscle strength test were accurate; specifically, the joint movements and the measured torques of the master and the slave robots were similar. This was possible because the movement speed of those tasks was slow enough to not be affected by the maximum time delay; however, the spasticity assessment was conducted with a fast speed (maximum stretching speed of 210°/s), and the time delay significantly degraded the haptic performance. It is possible that the amount of time delay can be significantly reduced, and we hope that this would improve the performance of fast tasks. With 5G technology being implemented worldwide, data transfer speeds are expected to increase. In addition, considering that we had to use a virtual private network to deal with the Internet security issue at the hospital, the data transfer could be faster if the hospital were to open an Internet gateway allowing for a direct connection between the two places.

The disagreement in the remote spasticity assessment could also come from the characteristics of MAS, the measure of spasticity used. In contrast to ROM and MRC, the inter-rater reliability of MAS has been known to range from poor to fair (28, 29). The MAS scores from the in-person assessment and the teleassessment had fair agreement in this study (k = 0.308), and this was within the range of the reported inter-rater reliability of the MAS scoring system (30, 31). Hence, two clinicians who participated in South Korea and the USA could rate different MAS even though the telerobotic system provides ideal haptic performance.

In this study, we did not evaluate the test-retest and inter-rater reliabilities of the proposed remote assessment. We expect that the reliabilities would be comparable with in-person assessment,

but the effect of degraded haptic feeling with different raters must be investigated. There was no qualitative evaluation (i.e., questionnaires on satisfaction) of the proposed assessment compared with in-person assessment. Finally, the proposed assessment was verified with small numbers of clinicians and stroke patients. Therefore, further research including cost analysis with larger sample sizes is required.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available from the corresponding authors on request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board at Seoul National University Bundang Hospital (IRB approval No.: E1101/058-001). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

H-SP, KC, and N-JP conceived the study idea and coordinated the study. JK, MS, and DP developed the telerobotic system. H-SP and KC supervised the engineering development. H-SP, JK, MS, Y-SM, DP, and WK involved in the experiments. JK, Y-SM, and WK analyzed the data. JK and W-SK drafted the manuscript, and all authors revised the manuscript.

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Corrigendum: Remote Assessment of Post-Stroke Elbow Function Using Internet-Based Telerobotics: A Proof-of-Concept Study

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H-SP, KC, and N-JP conceived the study idea and coordinated the study. JK, MS, and DP developed the telerobotic system. H-SP and KC supervised the engineering development. H-SP, JK, MS, Y-SM, DP, and WK involved in the experiments. JK, Y-SM, and WK analyzed the data. JK and W-SK drafted the manuscript, and all authors revised the manuscript.

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Feasibility Analysis of CareToy-Revised Early Intervention in Infants at High Risk for Cerebral Palsy

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Infants with perinatal brain injury are at high risk for Cerebral Palsy (CP). Progresses in detection of early signs of brain injury and of CP allow early intervention (EI) programs for improving the outcome of these infants. CareToy system (CT), developed within a European project (Trial Registration: NCT01990183), allows providing, by means of tele-rehabilitation, a highly personalized, family-centered, home-based EI for young infants, remotely managed by clinicians. CareToy, already used with pre-terms without brain injury, has been adapted for high-risk infants in a project funded by the Italian Ministry of Health, and the CareToy-Revised (CareToy-R) has been realized (Trial registration: NCT03211533 and NCT03234959). Before assessing its efficacy, it was crucial to evaluate the acceptability, usability, and feasibility of CareToy-R EI. Nineteen high-risk infants with perinatal brain injury, aged 5.95 ± 2.13 months (range 3.12–10.78 months), carried out an 8-week training with CareToy-R at home, performing customized playful activities with their parents, tailored to their rehabilitative needs, remotely managed by clinicians. The feasibility of training and study procedures was assessed through criteria derived from literature; acceptability and usability have been analyzed from data about individual training and an *ad hoc* questionnaire. All CareToy-R trainings were planned by the clinical staff with a daily personalized use for each infant between 30 and 45 min (mean 34.37 min). The amount of executed training by the infants was very high (daily mean 30.30 min), with no differences related to infant age, sex, and gestational age. All the nine feasibility criteria were achieved, family compliance to the project was very good, data collection was completed and the CareToy-R system worked properly and easily for parents. The answers to the questionnaire had a total mean score of 84.49% and they ranged from a minimum of 81.05% (in "easy to use" area) to a maximum of 86.49% ("changes due to the training" area), with no differences related to nationality or familiarity with technology of the mothers. This study reports preliminary evidence to the

feasibility of a home-based EI with CareToy-R system in infants at high risk for CP. Results of the RCT will provide data about the potential effectiveness of this approach.

Keywords: early intervention, tele-rehabilitation, CareToy, information and communication technologies, infants, cerebral palsy

INTRODUCTION

Perinatal brain injury exposes infants to a high risk for developing cerebral palsy (CP), the most common cause of physical disability during the developmental age (1). Despite recent evidence of a genetic contribution to the pathogenesis of CP, the presence of an early brain injury still represents the most important causative factor (2).

Typical care pathways for infants born preterm or with congenital brain injury consists of dedicated neuroradiological and clinical follow-up programs which can be established if the infant is at high risk for developing a CP (3). Indeed, the combined predictive power of magnetic resonance imaging (MRI) and clinical assessment tools such as the General Movement Assessment (GMA) according to Prechtl or the Hammersmith Infant Neonatal Examination (HINE) allow establishing a diagnosis of CP as early as 3–5 months with high sensitivity and specificity (3–5). An early and accurate diagnosis of CP is crucial as it allows a prompt and individualized access to a rehabilitative intervention program in a critical period for brain development; this promptness allows maximizing the effectiveness of intervention, exploiting a window of maximal plasticity for many different developmental domains (motor, visual, cognitive…) (6).

In order to be maximally effective, an early intervention program (EI) should be intensive, personalized, family-centered, and affordable both for families and health services. Moreover, EI should include multi-axial activities targeting motor, cognitive, sensory, and social functions in an integrated systemic approach (7).

The recent availability of tele-rehabilitation tools has allowed the application of this rehabilitative approach to the home setting which is the most enriching and ecological environment for the infants (8). Moreover, the possibility of standardizing a methodology of intervention and of remotely acquiring quantitative measure during the EI program, thanks to biomechatronic toys and telemonitored systems, has created a promising opportunity for developing innovative EI programs. The home-based concept and the tele-rehabilitation architecture provide significant added value to EI programs and both represent the pillars of the CareToy (CT) system.

The CareToy system was created in the framework of a multicentric international project (www.caretoy.eu, Trial Registration: NCT01990183). It is a biomechatronic baby gym equipped with different types of sensors designed to provide a highly personalized, family-centered, home-based intervention for young infants, remotely managed by dedicated clinical and rehabilitation staff. CareToy has been validated in an RCT study involving a sample of Italian and Danish preterm infants at low risk for cerebral palsy (9): results showed an improvement of the visual and motor development, as well as a maternal reduction of levels of stress (10). In a feasibility study, an EI program using CareToy has been carried out in a small population of infants with Down Syndrome showing the good adaptability of the system to different populations (11).

Basing on this experience, an EI program using a revised version of CareToy system (CareToy-Revised, CT-R) has been implemented in an ongoing RCT involving high-risk infants with perinatal brain injury (Trial registration: NCT03211533 and NCT03234959) (12).

Before analyzing the clinical efficacy of the CareToy-R system on this population, the present study aims to investigate the rate of acceptability, usability, and feasibility of an EI based on CareToy-R in families with infants at high risk for cerebral palsy.

MATERIALS AND METHODS

This feasibility study is focused on the upgraded version of CareToy, the biomechatronic smart baby gym, that is, the CareToy-R, designed and adapted for infants with perinatal brain injury, at high risk for developing CP.

The study protocol of the RCT project and the detailed description of the system have been published elsewhere (12). The wide CareToy-R RCT study is a multi-center, paired, and evaluator-blinded study with two investigative arms of two EI: Infant Massage and CareToy-R training for a duration of 8 weeks, in which eligible infants are allocated randomly at baseline (T0). Details are shown above.

The study has been approved by Tuscany Pediatric Ethics Committee (84/2017), and it was registered (NCT03234959) on Clinical Trials.gov.

Before comparing the effects of the Infant Massage and CareToy-R training, the feasibility, acceptability, and usability of the CareToy-R system need to be investigated.

Participants

Families of the subjects involved in this study were approached during the hospitalization in the Neonatal Intensive Care Units or during the neurodevelopmental follow-up programs in three different University Hospitals: the "Santa Chiara Hospital" in Pisa, the "Meyer Children's Hospital" and the "Careggi General Hospital," both in Florence.

For the CareToy-R study, infants with any sign of perinatal brain injury upon neonatal brain ultrasonography (US) or magnetic resonance imaging (MRI) were considered eligible. After 3 months corrected age, all the infants were checked for the presence of atypical clinical signs (absence of physiological fidgety movements or abnormal score at the Hammersmith

Infant Neurological Examination, HINE). The presence of both the clinical and the radiological criteria was considered mandatory in order to establish the high risk of CP and to offer the participation to the trial. The presence of polymalformative syndromes, cerebral malformations, severe sensory impairments (retinopathy of prematurity grade >II, deafness, or blindness) was considered exclusion criteria.

Parents or legal representatives signed the informed consent forms to accept the inclusion of the infant in the study. Recruitment for this preliminary study on feasibility started after the approval of the research project by the Ethics Committee. Intervention could start when the infant reached some pre-established motor skills (starting from the initial head control), which are expressed by the cut-off score of gross motor area of the Ages & Stages Questionnaire (last additional criterion).

For this feasibility study, eligible families were those of infants randomized to the CareToy-R arm of the project.

Study Design and Procedures

The recruitment of the whole CareToy-R project has started on September 2017 and has been completed on June 2020.

The minimum sample size required was 19 for the CareToy-R group.

After the enrolment, infants were allocated to one of the two investigative arms: CareToy-R training or Infant Massage [for details see Sgandurra et al. (12)]. Both interventions lasted 8 weeks and during this phase infants continue to receive standard care provided by National Health System.

Assessments, already described in the study protocol (12), were performed by a child neurologist and a therapist at the following times:

i) T0, the baseline, in the week before CareToy-R training or Infant Massage
ii) T1, the primary endpoint, within a week after the end of the training
iii) T2, after 8 weeks after the end of the training
iv) T3, last follow-up, at 18 months of (corrected) age of the infant.

The Infant Motor Profile [IMP, (13, 14)], primary outcome measure of the RCT CareToy-R study, is a video-based assessment of motor behavior of infants. Peabody Developmental Motor Scales—Second Edition [PDMS-2, (15, 16)], Bayley Scales of Infant Development [BSID-III, (17)] Cognitive subscale, standardized video-recordings of parent-infant interaction (18, 19), Teller Acuity Cards® (20), and Actigraphic analysis [Motionlogger Microwatch, (21)] were included as secondary measures. In addition, two questionnaires were administered to parents at all assessment times: BSID-III social-emotional scale (22) and Parenting stress index [PSI, (23)].

These assessment tools were administered at all assessment times.

Finally, families allocated to the Caretoy-R arm of the study were asked to fill in two questionnaires: the familiarity with technology (24) and "CareToy-Revised Questionnaire Parent-Infant Experiences" (see details below).

This last questionnaire, related to the feasibility aim, will be the measure reported in this study.

Intervention

CareToy-Revised System

CareToy is a technological smart system equipped with sensorized toys, developed as a telerehabilitation tool for home EI.

As described in literature (25, 26), it is a biomechatronic gym, composed by: (i) two feedback walls containing button, wires for toys, lights and speakers; (ii) a wall with a screen where specially developed pictures and videos are shown; (iii) a wall for the positioning of sitting posture modules; (iv) sensorized toys with different shapes; (v) an arch with lights and wires for toys; (vi) videocameras for recording infant's behavior; (vii) a sensorized mat; (ix) a kit of wearable sensors; and (x) a laptop with an *ad-hoc* software.

As described in the study design paper (12), in order to be adapted to the new population of infants, while maintaining the flexibility and variability of the proposals, the clinical staff planned to make some small but essential modifications to the CareToy system, creating the CareToy-R system.

First of all, due to the crucial postural needs of these infants, a postural modular system was added in the gym. An *ad-hoc* kit of Velcro-strap pillows was realized, using Siedo & Gioco facilities (Fumagalli, Italy), allowing a safe and comfortable positioning of infants in supine, prone, sitting, or side position, with different facilities (see **Figure 1**).

Together with this structural modification, the content of the goal-directed activities, called CareToy scenarios, was also changed. In detail, thanks to the possibility to set the audio-visual stimuli, the duration, intensity, and features of lights and sounds presented as stimulations and/or feedback have been modified.

Moreover, the video library was changed, adding some pictures and short movies with high contrasted images and customized features, useful for those infants with visual impairments.

The scenarios library was also modified and the clinical and rehabilitative staff made it more functional for the target population. Then, as in the previous projects, CareToy scenarios were further adapted to the individual developmental needs. Indeed, the training can be designed with high complexity and variability depending on the activated modules and features of lights, sounds, videos, and feedback. Scenarios could be planned to train the infant in different positions (supine, sitting, prone, on side), remotely chosen and periodically updated by rehabilitative staff according to infant's needs and capabilities, to promote the personalized goals.

After the T0 assessment, the CareToy-R system was delivered at home of infants randomized to the CareToy-R group; families who did not have an available internet connection were provided with a portable wi-fi router.

In general, the training was planned for 8 weeks, with daily activity between 30 and 45 min, organized in different scenarios (with different goals) lasting from 2 up to 10 min each. The first days of training were planned based on the baseline assessment;

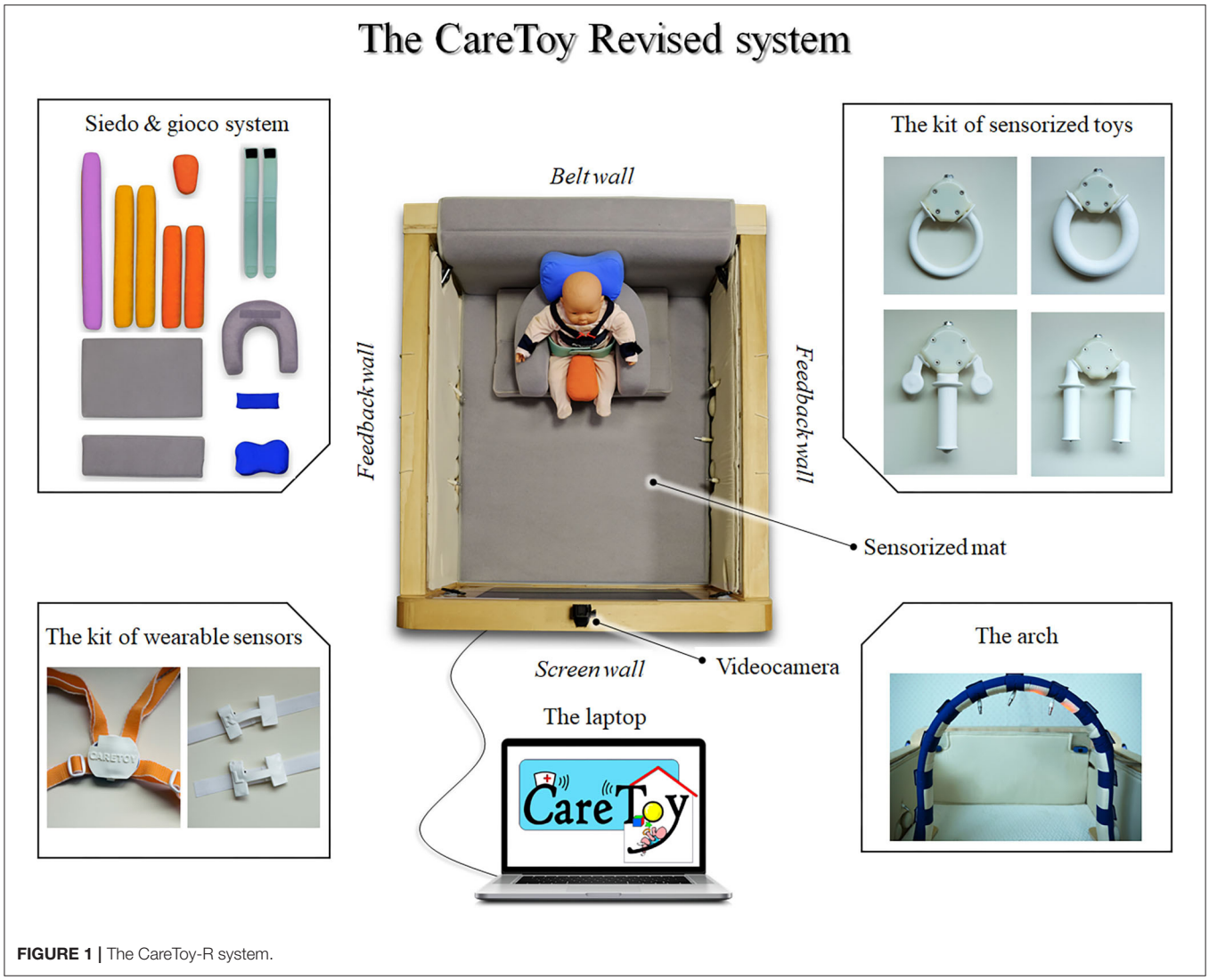

FIGURE 1 | The CareToy-R system.

then, therapists from remote periodically updated the training, according on infant behavior and/or progress.

Clinical and rehabilitative staff, mainly composed by child neurologists and pediatric physical therapists, followed infants and their families during the whole training period and planned and monitored the customized goal-directed rehabilitative activities called CareToy scenarios; parents were trained on how to use the system and how to play with their infant during the first days of CareToy-R intervention with face-to-face visits with therapists. During the whole training, the research team remotely monitored infants and performed on-site visits on a weekly basis. Additional assistance, with supplementary visits or video calls managed by clinicians together with the technical assistance supplied by bioengineers when necessary, was arranged as required, in order to provide hardware and software support and any additional advices on how to manage the training.

The CareToy-R project was active also during the COVID-19 pandemic period with three trainings provided during the forced lockdown; in these cases, on-site visits were replaced by tele-visits and regular staff meetings were performed online.

Outcome Measures

The feasibility of CareToy-R training has been evaluated on several measures.

Feasibility Criteria

The criteria, based on relevant recommendations for conducting research on feasibility, have been taken from the literature (27–29). The feasibility measures were grouped on the basis of their focus which could be the training intervention or the procedures and study design.

These criteria have been adapted for the CareToy-R study; in details measures have been established as follows:

Feasibility of intervention:

✓ Accessibility: intelligibility of information of the scenarios in terms of preparation (use of pillows, toys, etc.) and execution

(how to stimulate infant), showed on parents' interface of the laptop
- ✓ Training compliance: required days for completing the 80% of the planned training (at least 8 weeks, that is, the fixed interval of the training)
- ✓ Technical smoothness: good functioning of the CareToy-R system, defined as the quantity of technical issues and malfunctioning experienced
- ✓ Training motivation: motivation and reported effort in carrying out the training.

Feasibility of study design and procedures:

- ✓ Participation willingness: rate of acceptance of the participation in the study
- ✓ Participation rates: number of dropouts
- ✓ Loss to follow-up: recording of all data from all outcome measures
- ✓ Assessment time scale: required interval for collecting all outcome measures (at least 1 week)
- ✓ Assessment procedures: loss to follow-up rates.

The definition and measurement of CareToy-R feasibility criteria is shown in the **Table 1**.

The Questionnaires

Considering the crucial role of parents in CareToy-R intervention, it was necessary to assess their ability to use the system and their perception about system usage and training effectiveness. For this reason, all families were asked to fill in two questionnaires, aimed to understand their familiarity with technology and their opinions about the training.

The first tool is a questionnaire already available in literature, that is, the Information Technology (IT) Familiarity Questionnaire, developed by Geyer (24). It has been used to evaluate the participants' familiarity with Information Technology. It consists of 8 questions in 3-points Likert scale (1=daily use, 2=seldom use, 3=never used), investigating the frequency of use of IT. The total score was the average of the scores of the eight questions. This first brief questionnaire was aimed to understand the familiarity with technology of parent who mainly carried out the training.

The second tool is an *ad-hoc* questionnaire called "CareToy-Revised Questionnaire Parent-Infant Experiences (CRQPE)," developed from the acceptability questionnaire of the first CareToy project [(30); see **Supplement 1**]. It is organized in 44 questions, divided in five areas: general features of CareToy-R system, changes due to the training, easy to use, infant participation, and time dedicated to the training. It is mainly composed by Likert scale answers in five points (where 1 meant "not at all," up to 5 which meant "yes") and there are also some open answers in which parents can express their thoughts. All the items of CRQPE were developed, specifically for CareToy-R project, out of the standard definitions of usability (31–33) and acceptability (34, 35).

The two questionnaires were administered in the post-training assessment (T1).

Data Collection

The clinical staff remote management of the training was possible thanks to the software CareToy Admin, which allows to plan the training choosing scenarios from the library and/or to modify them for a more suitable use for the single infant. Moreover, CareToy Admin collects all the training sessions and automatically provides a detailed report which includes planned and details of executed scenarios. Clinicians have the possibility to check all data of the modules (e.g., sensorized toys, mat, etc.) and the videos of infant play, for specific analyses, detecting the results and planning further training.

At the end of each training, a Microsoft Excel sheet is created, summarizing planned and executed scenarios together with the duration of each scenario, each session (training day) and of the whole training.

The questionnaires were administered to families immediately after the end of the CareToy-R training period (T1) in a face-to-face interview with the parent who was mainly in charge of the training (or both). This allowed an easier administration, as the interviewer was free to explain the questions when necessary and, above all, it gave the opportunity to parents to explain their opinions.

Statistical Analysis

Clinical data were analyzed by means of Statistical Package for Social Sciences (SPSS, vers. 20.0). Descriptive analyses were used to show the demographic data of infants and of their mothers and the results of questionnaires, for the different areas and the total. Next, multivariate analyses were carried out to explore the differences of treatment planning (i.e., Mean daily CareToy-R training planned in minutes and Total planned training in hours) and of treatment execution (i.e., Mean daily CareToy-R training executed in minutes and Total executed training in hours) and of the total scores and the different domain scores of the CRQE in relation to the infant's and mother's factors. Specifically, for infants, we considered the age at T0 as covariate and the sex (male/female) and the gestational age (prematurity/at term) as fixed factors. For the mothers, we considered the values of "familiarity with technology" as covariate and the nationality (Italian/Foreign) as fixed factor. Moreover, as exploratory analyses, the Mann-Whitney *U*-test was carried out to compare the hours of total training planned and executed in the infants that did the CareToy-R training during the lockdown period respect to the others.

RESULTS

Participants

Among the 20 eligible families randomized to the CareToy arm of the RCT, 19 families agreed to participate to the intervention. All participants included in the CareToy-R intervention investigative arm of the CareToy-R project (total: 19 families) accepted to fill in the two questionnaires.

Fourteen families were Italian while five from foreign countries (2 Polish, 1 Albanian, 1 Peruvian, and 1 Ukrainian). Trainings were carried out in different districts of Tuscan region with a mean distance of 79.8 km from IRCCS Fondazione Stella

TABLE 1 | Feasibility criteria.

	Feasibility criteria	Definition	Feasibility question	Feasibility criterion for success	Measurement/recording?
Feasibility of intervention	Accessibility	Intelligibility of information of the scenarios preparation (pillows, toys, etc.) and execution (how to stimulate infant), showed on CT-R interface	Do participants understand all training objectives and rules?	100% of participants understand all activities of the training	Recording of clarification requests to the therapist, number of error message displayed on the laptop
	Training compliance	Duration of the training (at least 8 weeks, that is, the fixed interval of the training)	Do participants perform all training sessions in at least 8 weeks?	A minimum of 80% training completed in 8 weeks	Report from CareToy Admin, i.e., the date of the first and the last day of training
	Technical smoothness	Functioning of CT-R system, defined as the quantity of issues and malfunctioning	Are there technical issues with the training?	90% of participants will be able to perform their training without technical issues	Number of assistance requests
	Training motivation	Motivation and reported effort in carrying out the training	Are participants motivated to perform training intervention?	Difference between planned training days and executed training days	CareToy admin data about planned and executed training
Feasibility of study design and procedure	Participation willingness	Rate of acceptance of participation in the study	What is the participation rate?	At least 80% of eligible participants agreed to join the project	Caretoy database
	Participation rates	Number of dropouts	Do all eligible participants who agree actually perform the training intervention?	80% of participants who gave consensus participated in the study	Caretoy database
	Loss to follow up	Recording of all data from all outcome measures	Can all data be collected without any problems?	90% of the outcome measures were collected	Caretoy database
	Assessment time scale	Required interval for collecting all outcome measures (at least 1 week)	Can follow-up data be collected within a week after the training period?	Time from end of training period to first follow-up data collection	Recorded data of the beginning and the end of the training (CareToy Admin) and data of assessments
	Assessment procedures	Loss to follow-up rates	Is the loss to follow-up acceptable?	Less than 20% of participants fail to complete outcome measures on all follow-up assessments	Collection of data report by examiners

Maris, ranging from Pisa (15 km, the nearest place from Stella Maris) to Arezzo (165 km, the farthest).

The sample of infants was composed by 11 males and 8 females, with a mean age at the beginning of the study of 5.95 ± 2.13 months (range 3.12–10.78 months).

The trainings were assisted exclusively by mothers and their mean age was 32.95 ± 6.49 years (range 18–41 years). Most mothers were employed at the time of the training and had a high school education.

Demographic characteristics of participants (infants) and mothers are shown in **Table 2**.

Feasibility Outcome

Feasibility criteria were all achieved as follows.

First of all, the Feasibility of Intervention:

- ✓ Accessibility: all participants completely understood instructions presented with software and written on printed manual; there were no further requests of clarification. Furthermore, variables related to mothers, as the nationality or the results of the questionnaire "familiarity with technology" did not impact the dose of executed training (**Table 3**).
- ✓ Training compliance: the clinical staff, on the basis of each infant's developmental need and personal goals, scheduled all the trainings for a total duration of 33 to 55 days, planning a mean daily training which ranged from 27.90 to 39.27 min (mean 34.37 ± 3.15 min) (**Table 4**). The period of forced lockdown (#2, #12, and #19) due to the emergency of COVID-19 pandemic, did not change the way to plan and deliver the training, and even if not significantly, the total planned and executed training (hours) was higher in the three cases carried out during COVID-19 (28.29 ± 1.53 and 26.42 ± 2.92, respectively) with respect to the others (24.47 ± 4.69 and 21.60 ± 5.28, respectively).

Considering different variables as corrected age of infant at the beginning of the training, sex, and gestational age (expressed as preterm or at term), there were no significant differences in the planned number of days of training and in the planned daily mean duration of the training (**Table 4**).

All participants completed the training with a total duration of 31 to 55 days (mean 43.21 ± 7.67), carrying out a mean daily training which ranged from 21.34 to 35.83 min (mean 30.30 ± 4.42). The mean total duration of the performed training was 22.40 ± 5.15 h (**Table 5**).

All participants completed the 80% of training in 8 weeks; only four participants needed one extra week to complete the training (total duration: 9 weeks) and this was mainly related to holiday periods.

Moreover, when considering the executed amount of training, there were no significant differences related to the variables: age at the beginning of the training, sex, and gestational age.

TABLE 2 | Sample characteristics.

ID	Gestational Age (weeks)	Infant Age at T0 (months)	Sex	Mother age (years)	Mother nationality
#1	40^{+5}	4.34	Female	34	Italian
#2	37^{+5}	4.67	Female	41	Polish
#3	26^{+0}	10.59	Male	36	Italian
#4	40^{+0}	6.48	Male	35	Italian
#5	32^{+4}	6.12	Male	41	Italian
#6	40^{+0}	7.56	Female	36	Italian
#7	40^{+0}	5.75	Female	28	Italian
#8	26^{+0}	6.84	Female	35	Italian
#9	36^{+3}	4.50	Male	31	Italian
#10	33^{+0}	5.00	Female	29	Italian
#11	40^{+0}	8.68	Male	37	Italian
#12	37^{+0}	4.54	Male	26	Italian
#13	39^{+0}	4.96	Female	24	Polish
#14	27^{+0}	3.12	Male	27	Albanian
#15	40^{+0}	4.27	Male	39	Italian
#16	26^{+6}	5.92	Male	39	Italian
#17	29^{+0}	10.78	Male	18	Peruvian
#18	40^{+0}	4.27	Female	29	Italian
#19	40^{+0}	4.64	Male	41	Ukrainian
Group results	35.16 ± 5.68	5.95 ± 2.13	11 males 8 females	32.95 ± 6.49	14 Italian 5 foreign

TABLE 3 | Mothers characteristics.

	Nationality (Italian or foreign country)			Questionnaire "familiarity with technology"		
	F-test	Df	*p*-value	*F*-test	df	*p*-value
Mean daily CT-R training planned (minutes)	0.043	1	0.839	0.146	1	0.708
Mean daily CT-R training executed (minutes)	1.230	1	0.284	0.014	1	0.907
Total planned training (hours)	2.032	1	0.173	3.416	1	0.083
Total executed training (hours)	2.890	1	0.108	1.661	1	0.216

- ✓ Technical smoothness: the CareToy-R system experienced two kinds of hardware issues: in one case, it was necessary to replace during the training the laptop of the Caretoy system and in 12 families one of the toys. The software presented some technical issues during 3 trainings. Nevertheless, all these issues were fixed with a remote assistance by a dedicated team of engineers; after a quick replacement of the malfunctioning item, all participants could resume the training after a stop of about a half day.
- ✓ Training motivation: 12 subjects executed the 100% of the planned training days and the other seven subjects between 96 and 99% of the planned training days.

Concerning the feasibility of study design and procedures:

- ✓ Participation willingness: only one eligible family did not give the consent in participating to the project, because they have not the required space in their house for positioning the CareToy-R system.
- ✓ Participation rates: No dropouts were reported.
- ✓ Loss to follow-up: it was possible to record all data of all outcome measures and there were no missing data.
- ✓ Assessment time scale: follow-up measurements of all participants were collected within 1 week after the end of the training (range 0–7 days, mean= 4.53 ± 3.31 days). Only three follow-up measurements were collected between 8 and 15 days after training, because of the holiday period (mainly summer holiday and Christmas).
- ✓ Assessment procedures: all participants who started the training intervention completed the post-training assessments.

The Questionnaire

All 19 families accepted to fill in the questionnaires and the interview was carried out by therapist during the assessment after the training (T1).

Overall, the answers of the CRQPE questionnaire had a total score all above 110 points (corresponding to 73.33%) with a range of 110–138 points and mean total score of 126.74 ± 8.43 points (84.49%).

Regarding the five sections: "Infant participation" had a range of raw scores between 19 and 30 points, "Easy to use" had a range of raw scores from 21 to 27; the section "General features of CareToy-R system" presented a range from 22 to 29 and "Changes due to the training" showed a range from 21 to 30 and "Time dedicated to the training" between 20 and 29.

In the subsections the percentage of mean raw scores resulted in increasing order: 81.05% in "easy to use" (low percentage obtained), 84.74% in "general features of CareToy-R system," 84.91% in "time dedicated to the training," 85.26% in "infant participation," and 86.49% in "changes due to the training" (higher percentage obtained).

Median and 95% confidence interval of scores in the questionnaire (both total and section scores) are shown in **Table 6** and **Figures 2**, **3**.

Furthermore, the answers of (IT) Familiarity Questionnaire (24) had a raw score range between 8 and 21 points (33.33–87.50%) and mean total raw score of 12 points (51.32%). The total mean presented a range between 1.00 and 2.63 points.

There were no significant effects in the total scores and different sections of CRQPE respect to the sex of the subjects, the age at the beginning of the training, or the gestational age (**Table 7**).

Likewise, there were no differences in the total scores of answers related to mothers' characteristics: nationality and the level of familiarity with technology (**Table 8**).

DISCUSSION

The present study is the first one in the literature that investigates the acceptability, usability, and feasibility of CareToy-R EI in families with infants at high-risk for CP, evidencing the first

TABLE 4 | Infants characteristics and training.

	Age at T0			Sex (male and female)			Gestational age (preterm or term)		
	F-test	df	*p*-value	*F*-test	df	*p*-value	*F*-test	df	*p*-value
Mean daily CT-R training planned (minutes)	1.402	1	0.256	0.004	1	0.951	0.208	1	0.656
Mean daily CT-R training executed (minutes)	0.318	1	0.582	2.250	1	0.156	0.100	1	0.756
Total planned training (hours)	1.592	1	0.228	0.069	1	0.797	1.217	1	0.289
Total executed training (hours)	1.049	1	0.323	0.637	1	0.438	0.358	1	0.559

TABLE 5 | CT-R training data.

ID	CT-R Training days planned (N°)	CT-R Training days executed (N°)	Training executed (%)	Mean daily CT-R training planned (minutes)	Mean daily CT-R training executed (minutes)	Total planned training (hours)	Total executed training (hours)
#1	42	38	96%	35.72	23.06	25.01	16.14
#2	55	55	100%	32.20	31.35	29.51	28.74
#3	33	33	100%	39.26	35.64	21.59	19.60
#4	48	48	100%	38.44	35.83	30.75	28.66
#5	33	31	98%	33.52	29.84	18.43	16.41
#6	35	34	99%	27.90	21.34	16.28	13.31
#7	51	51	100%	34.62	31.10	29.43	26.43
#8	43	43	100%	37.56	28.60	23.59	20.49
#9	50	50	100%	34.46	34.34	28.72	28.62
#10	46	43	97%	31.65	26.52	24.26	20.33
#11	50	50	100%	36.36	33.73	30.30	28.11
#12	50	50	100%	31.88	27.77	26.57	23.14
#13	44	42	98%	39.27	34.67	29.45	26.00
#14	50	50	100%	33.79	32.30	28.16	26.92
#15	41	39	98%	28.85	22.40	19.72	15.31
#16	35	35	100%	35.99	34.46	20.99	20.10
#17	33	33	100%	35.07	31.97	19.29	17.58
#18	45	43	98%	33.99	29.85	25.49	22.39
#19	53	53	100%	32.59	31.02	28.78	27.40
Group results (mean±SD)	44.05 ± 7.28	43.21 ± 7.67	99% ± 1%	34.37 ± 3.15	30.30 ± 4.42	25.07 ± 4.54	22.40 ± 5.15

milestone in the field of the use of new medical devices in tele-rehabilitation. It is crucial that a new device that is addressed to the home use is feasible in its use because even if it is effective but not feasible, it is hard to be used and translated in the clinical practice. With the current study, we have shown for the first time the applicability of the CareToy-R system and its relevance for home-based early intervention programs in high-risk infants.

For our purpose we referred to the literature for the indication about the methods to assess the usability and acceptability of technologies for home-based rehabilitation (36) and the criteria based on relevant recommendations for conducting research on feasibility, already used in studies (27–29, 37).

The data of this feasibility study highlight different achievements and are in line which the principle of high customized training of the CareToy concept.

Since the first CareToy has been created, many studies have been dedicated to test its effects on preterm infants (9) and its feasibility in other populations (11); the current study presents the first results concerning its feasibility in another delicate population, namely, infants with perinatal brain injury. As compared to the previous CareToy studies, this project not only involves a new and critical population but also introduces some change in the CareToy system and the extension up to 8 weeks of the training duration.

The high rate of acceptance of the CareToy-R project is the first interesting data, which means that the proposal has been agreed upon and the majority of families share this approach and trust the clinical staff in the importance of this EI approach. In one case, a family refused to participate in the project for the lack of enough room to install the CareToy in their house; this could represent a limit to overcome. The scale in which the CareToy-R system was realized was a compromise between the need of including many different sensors and technology and the need to guarantee enough space for the infant move freely; in a future perspective, the use of smaller sensors and hardware components could reduce the size of

CareToy, making it more suitable also for families who live in small apartments.

The use of tele-rehabilitation, together with the already known advantages of overcoming the limit of distances and maintaining patients in close contact with their therapists (38), allowed to guarantee the prosecution of the rehabilitation intervention also during the lockdown due to the COVID-19 pandemic emergency, without reducing the dose of the proposed training. The tele-rehabilitation architecture has recently gained much attention due to the possibility of delivering rehabilitative intervention also in periods in which access to healthcare facilities is limited, such as during the sanitary lockdown.

The results of this feasibility study on CareToy-R training confirmed the good functioning of the tele-rehabilitation architecture that in this specific project did not present the typical limit of the unstable or malfunctioning connection (39), thanks to the possibility of delivering a portable router which supplied internet access to those who did not have a personal one or whose connection did not have the required speed. Indeed, connectivity barriers often influence the experience of tele-rehabilitation of patients and clinical staff (40).

Within this project, only families who lived in Tuscany participated in the CareToy-R intervention, and this was due to the recruitment, carried out in the three Neonatology Units of the main Hospitals of this region. An interesting perspective could be to create a more national network, including several Neonatology Units, in order to offer the possibility to join the CareToy-R project also to infants who live in other regions, with the aim of standardizing the methodology and giving the same opportunity of a home-based EI also to infants who live far away from the main clinical centers.

Another first index of CareToy-R feasibility was represented by the clinical and rehabilitative staff management and planning of CareToy-R training and, in particular, by the possibility to program an 8-week training with a daily session of a minimum

TABLE 6 | Results of CRQPE questionnaire.

	Sample	
	Median [95% CI]	
	Raw score	%
General features of CareToy-R system	25.42 [24.49–26.35]	84.74% [81.65–87.83]
Changes due to the training	25.95 [24.53–27.36]	86.49% [81.78–91.20]
Easy to use	24.32 [23.53–25.10]	81.05% [78.43–83.68]
Infant participation	25.58 [24.19–26.97]	85.26% [80.62–89.91]
Time dedicated to the training	25.47 [24.15–26.79]	84.91% [80.52–89.31]
Total	126.74 [122.67–130.80]	84.49% [81.78–87.20]

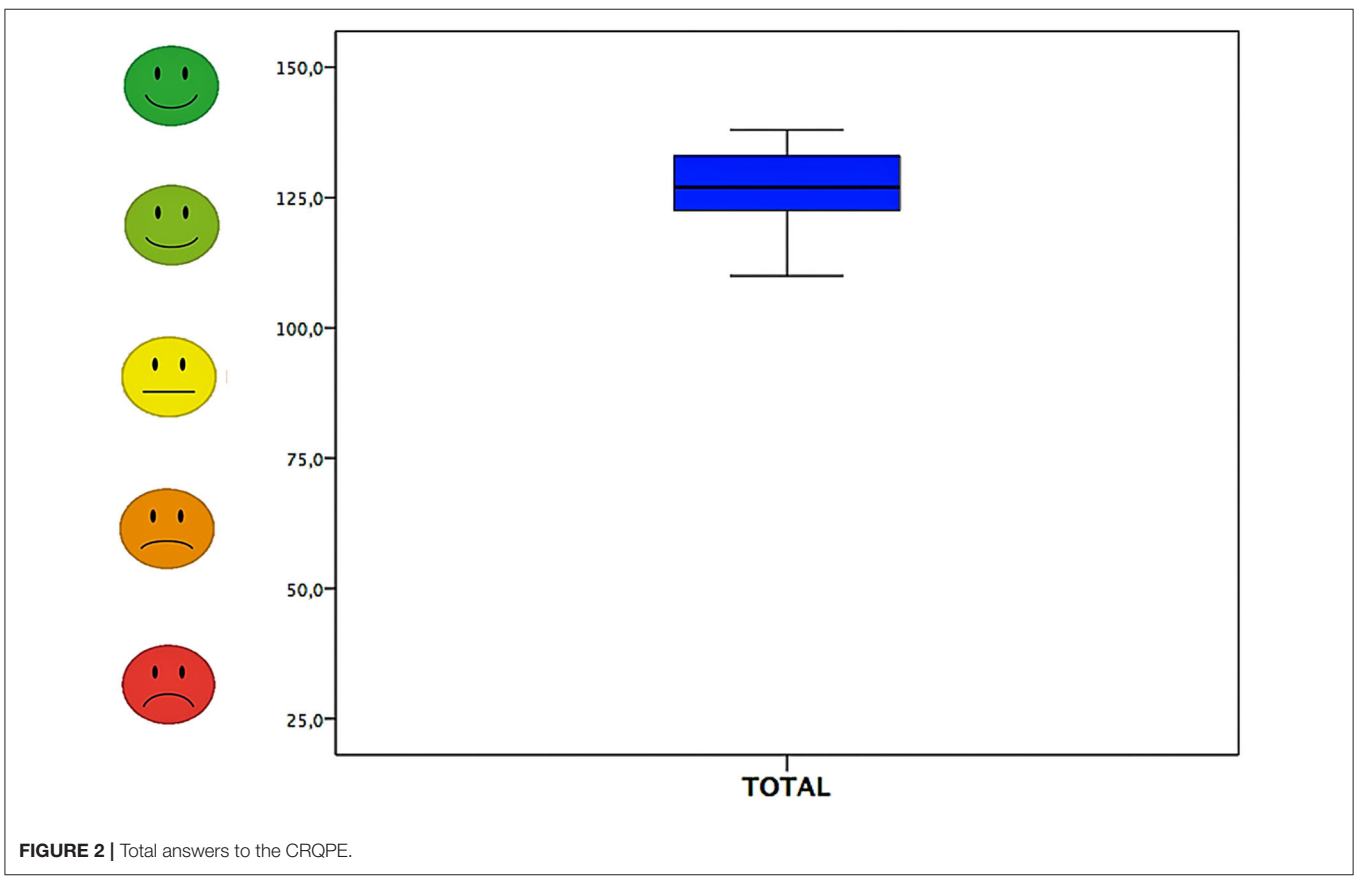

FIGURE 2 | Total answers to the CRQPE.

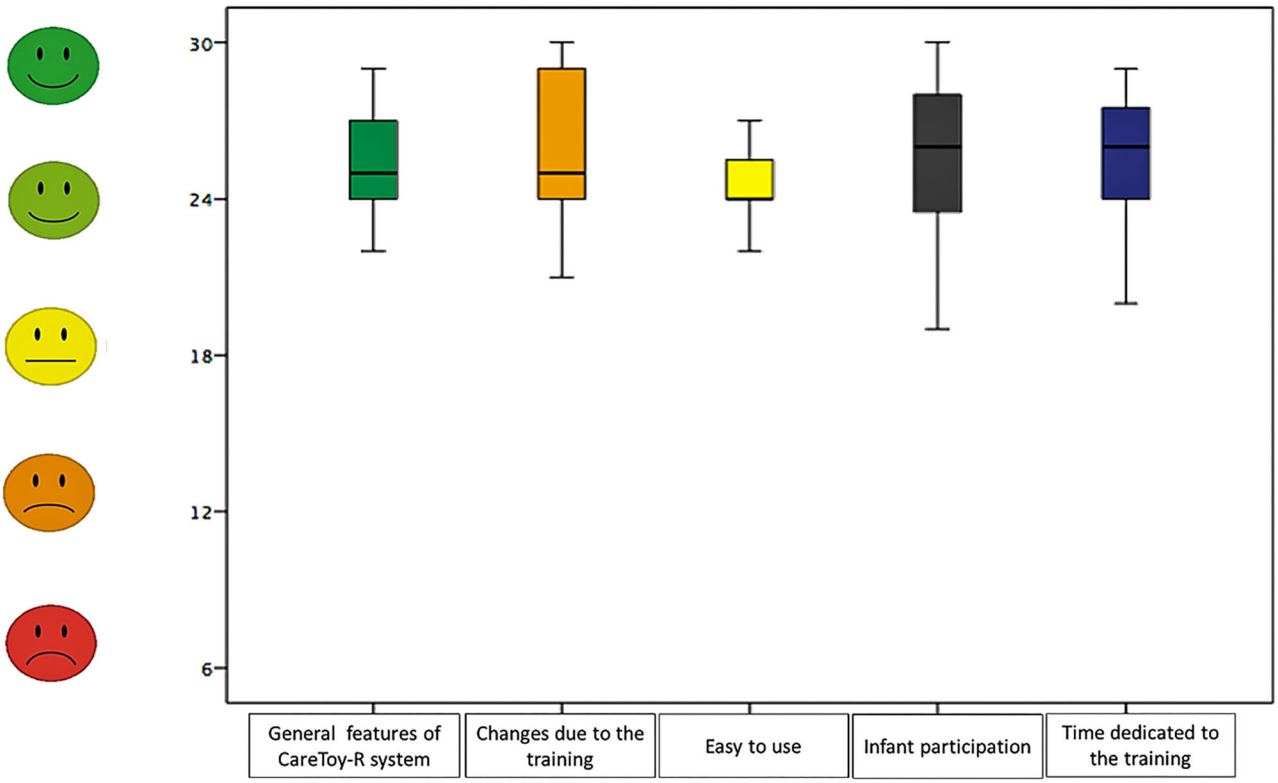

FIGURE 3 | Answers of CRQPE sections.

of 30 min. All the planned scenarios were addressed to meet each specific rehabilitation need; the absence of differences in the amount of planned training among infants who presented different clinical pictures confirms the appropriateness and the high personalization of CareToy-R scenarios.

On their side, families were very compliant also in performing the training. The familiarity of technology, generally high for our sample, seemed not to impact the amount of executed training; this means that the CareToy-R system has been shown as an easy-to-use platform, and the experience in using technological devices does not play a role in the usability of the system.

The high quantity of executed scenarios, not influenced even by the infants' characteristics (sex, gestational age and age at T0) further support the high customization and the focus on each single developmental need and goal of each participant.

As we know, the personalization is of critical importance and the underlying heterogeneity of many disease processes suggests that the strategies for treating an individual with a disease, and possibly monitoring or preventing that disease, must be tailored to match that individual's unique biochemical, physiological, and behavioral profile. This precision medicine, which is one of the new challenges of the research, is not a whole new approach, but it can represent an enhancement of an already used concept aimed to identify, assess, organize and analyze multiple variables to generate a precise and tailored approach. This is not an end-point process, but it includes a number of feedback loops which need ongoing efforts to become ever more precise. Patient data are used to develop clinically relevant models, and the results of these analyze then address the further assessment of patients, as an example of precision medicine as an evolving result (41–44).

In this framework, the CareToy approach showed to have a modular concept and it allows further upgrade for becoming a model of precision medicine, by adding specific and detailed quantitative measurements for each infant allowing a personalized functional profile of infants with different and specific needs.

It is also interesting to consider the dose of performed training together with users' satisfaction in using the system, because they are crucial factors to increase motivation and compliance. On the basis of the CRQPE results, the whole sample of 19 families willingly accepted to fill in the questionnaires and gladly accepted the interview, showing a very good level of acceptability and usability.

CRQPE has demonstrated the possibility of systematically and quantified parental opinions on different features of the CareToy project and the CareToy-R system.

The section "infant participation" had the lowest score, but the score meant that the involvement of the infant in CareToy scenarios was high; together with the high result of the section "changes due to the training" and the data about the amount of training, these data could confirm the suitability of the planned activities to each infant. The areas of the CRQPE relative to the "easy to use" and "general features of CareToy-R system" could be linked to the appreciation of the CareToy-R by families, which

TABLE 7 | Infants' characteristics and CRQPE answer questionnaire.

	Age at T0			Sex (mother and female)			Gestational age (preterm or term)		
	F-test	Df	*p*-value	*F*-test	Df	*p*-value	*F*-test	df	*p*-value
General features of CareToy-R system	2.638	1	0.127	0.899	1	0.359	0.039	1	0.901
Changes due to the training	0.921	1	0.354	0.005	1	0.947	0.016	1	0.836
Easy to use	1.058	1	0.321	2.002	1	0.179	0.044	1	0.614
Infant participation	2.012	1	0.178	0.887	1	0.362	0.358	1	0.752
Time dedicated to the training	1.058	1	0.321	0.156	1	0.699	0.104	1	0.683
Total CRQPE	3.233	1	0.094	0.469	1	0.504	0.174	1	0.846

TABLE 8 | Mothers' characteristics and CRQPE answer questionnaire.

	Nationality (Italian or foreign country)			Results of the questionnaire "familiarity with technology"		
	F-test	df	*p*-value	*F*-test	Df	*p*-value
General features of CareToy-R system	0.094	1	0.763	0.45	1	0.835
Changes due to the training	0.056	1	0.816	0.889	1	0.360
Easy to use	0.440	1	0.517	0.498	1	0.490
Infant participation	0.644	1	0.434	0.553	1	0.468
Time dedicated to the training	1.213	1	0.287	0.228	1	0.639
Total CRQPE	0.350	1	0.562	0.011	1	0.918

had experienced a simple use of the system and liked its features, both in terms of functionality and appearance. Furthermore, despite the variability of expertise in the use of IT, all families reported easy use and returned positive feedback about the feasibility of CareToy-R training, and this further confirmed the usability and acceptability of the CareToy-R system. Finally, the area "time dedicated to the training," which included questions related to the role of the parent while performing the training, had the highest score of all areas. This means that mothers (who mainly executed CareToy-R training) felt free and confident using the system; moreover, many of them reported that they thought to be empowered after the training. In this sense, the remote guide and support by an expert clinical staff seemed to yield benefits to the parental role.

Looking at the additional comments, the CareToy-R system showed to be, from the parental perception, a useful and innovative tool to promote the development of infants at high neurological risk. The CareToy-R system was indeed widely appreciated in several features by parents, who considered it useful in enhancing and promoting specific skills of their infants on the basis of their individual profile. Parents felt themselves totally involved in their infant's rehabilitation project and they shared activities and playful sequences that allowed them to discover their infant's abilities and potentialities.

Thanks to families' opinions raised from the CRQPE, the CareToy can be improved and optimized for different populations and it could be further be empowered in terms of acceptability and usability. This should support the motivation, encourage parents to perform the training with their infants and, as a consequence, maximize the efficacy of the intervention.

The results of the questionnaires have given an interesting insight directly from the families who participated to the project; this has been useful in order to get feedback on the adequacy of the system and on the appropriateness of the rehabilitation proposals. This vision will serve as an input in order to further improve the CareToy system, correcting those features which are considered less acceptable.

Out of the importance of this feasibility study, some limitations need to be underlined. First of all, concerning the study design, the participation of families in a RCT study and the previous positive results of the CareToy approach in low risk infants can represent a bias because their expectations could affect the answers in the questionnaire. Another bias could be related to the administration way of the CRQPE questionnaire that was carried out by the assessor therapist, blind to the intervention in terms of duration and progressions, as an interview. We chose this way to administer interviews to make parents more confident in talking about their experiences and adding personal comments to the Likert answers, but a positive bias could be raised. Moreover, we have investigated only the parents' point of view but there is the lack in having the feedback of all other end-users opinions than parents, e.g., it would be interesting to create a tool respecting the standard definition of usability and acceptability, aimed to collect data about the point of view of the rehabilitation staff. Moreover, it has not foreseen a detailed cost analysis in order to assess a cost-effectiveness analysis, crucial for estimating the real possibility that CareToy training could have a contribution to reduce the costs of health services and could become relatively inexpensive and can expand the accessibility of rehabilitation to infants at high risk for CP.

Besides these limitations, the current study constitutes the basis of the feasibility of the CareToy-R intervention in high-risk infants, and results of the RCT will show the efficacy of this approach in improving the outcome of this population.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Tuscany Pediatric Ethics Committee. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

GS and GC conceived the idea for this original research and all other authors contributed to the conception and the design of the study. AC, MC, MG, GS, GC, and RR carried out the enrollment of all infants for the study and their baseline neurological assessment and eligibility. EB, VM, and GS designed and realized the questionnaire. VM performed all the motor assessments and carried out the questionnaires. GS performed the statistical analysis. EB, GS, VM, GC, and RR conceived and prepared the manuscript. All the authors read, critically revised, and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

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REVIEW
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Telemedicine Guidelines in South East Asia—A Scoping Review

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Background: Telemedicine is a useful tool to deliver healthcare to communities in low- to high-income countries, especially in the coronavirus disease 2019 pandemic era. Guidelines on telemedicine would assist healthcare providers in delivering healthcare services based on local circumstances.

Objective: To explore and compare guidelines on telehealth and telemedicine in South East Asian countries.

Methods: Electronic databases such as Google, PubMed, and Cochrane reviews were searched for articles using keywords such as "telemedicine" OR "telehealth" OR "eHealth" OR "telemedis" AND "guidelines" AND "South East Asia" OR "Malaysia" OR "Singapore" OR "Indonesia" OR "Thailand" OR "Vietnam" published up to 2020. Inclusion criteria were full articles and gray materials (i.e., policy statements, advisories, blueprints, executive summaries, and circulars) related to telemedicine guidelines. No language restrictions were imposed. Only the first 100 Google searches were included for eligibility based on its relevance to telemedicine guidelines. Exclusion criteria were abstracts, duplicate publications, blogs, news articles, promotional brochures, conference proceedings, and telemedicine projects unrelated to telemedicine guidelines.

Results: A total of 62,300 articles were identified through the search engines (Google 62,203, PubMed 77, and Cochrane 20) and six articles from additional sources. Sixty-eight full-text articles fulfilled the inclusion criteria, but only 24 articles contained some form of guidelines on telemedicine: Indonesia (nine), Malaysia (seven), Singapore (five), Thailand (two), and Vietnam (one). There were six laws, six advisory guidelines, five policy statements, and two circulars (regulations) issued by either the Ministry of Communication and Multimedia, Ministry of Health, or Medical Councils from the respective countries. Issues addressed were clinical governance (100%); information and communication technology infrastructure (83.3%); privacy, storage, and record-keeping (77.8%, respectively); ethics and legal (77.8%); security and safety (72.2%); definitions and applications of telemedicine (72.2%); confidentiality (66.7%); licensing (66.7%); identification (55.6%); cost of information and communication technology infrastructure (55.6%); reimbursement (16.7%); mobile applications (11.1%); and feedback and choices (5.6%). The Singapore National Telemedicine Guidelines contained the most domains compared with other guidelines from South East Asia.

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Conclusions: Although there can be no "one-size-fits-all" telemedicine guideline, there should be a comprehensive and universal telemedicine guideline for any country to adapt based on the local context. Details on patient-identification, data ownership, back-up, and disposal; transregional cybersecurity laws and ways to overcome the limitations of telemedicine compared with face-to-face consultations should be outlined clearly to ensure uniformity of telemedicine service and patient safety.

Keywords: universal, low to high income countries, guidelines, telemedicine, South East Asia

INTRODUCTION

Telemedicine, telehealth, or eHealth is the delivery of health-care services using information and communication technology (ICT) in the diagnosis, treatment, and prevention of disease or injuries, research, evaluation, and education for health-care providers and their communities (1).

Telemedicine is an efficient and cost-effective way to deliver acute, chronic, primary, and specialty care (2–5). However, the overall uptake of telemedicine has been slow among health-care providers globally, as it has been an optional rather than mainstream form of health-care delivery before the coronavirus disease 2019 (COVID-19) pandemic (6). Common barriers include technically challenged staff, cost, lack of high-speed internet (7, 8), conflicting health system priorities (8), and lack of political will (9).

Recent policy changes during the COVID-19 pandemic (10, 11) have reduced barriers to telemedicine. Advances in digital technology have expanded mobile health (mHealth) (8) applicability from providing health care in remote communities (12–14) to situations where face-to-face consultation is neither safe (6) nor practical (8). The use of mHealth in South East Asia (SEA) has increased exponentially in the last decade as it is the world's fastest-growing market for digital economy (8). The COVID-19 pandemic has spurred the growth of telemedicine from telephone consultations to a spectrum of ICT applications. The diversity in telemedicine practice across countries calls for uniformity in guidelines and standards (15). Payers, regulators, and policymakers would refer to guidelines and legislations, especially if telemedicine were integrated into existing policies and standard care. This scoping review aims to compare telemedicine guidelines in SEA, as the region shares common social and economic conditions.

OBJECTIVE

This scoping review aims to explore and compare guidelines on telehealth and telemedicine in SEA countries.

METHODS

Literature searches were conducted from 1 January to 7 May 2020 using PubMed, Cochrane, Embase, and Google search engines published up to 2020 (**Figure 1**). A combination of relevant MeSH and Emtree terms and keywords related to "telemedicine" OR "telehealth" OR "eHealth" OR "telemedis" AND "guidelines" AND "South East Asia" OR "Malaysia" OR "Singapore" OR "Indonesia" OR "Thailand" OR "Vietnam" was used. Records identified through database searching were screened for duplicates using the reference management software Mendeley. Additional sources were obtained through advisories and guidelines issued by the Ministry of Health and Medical Councils of Malaysia, Indonesia, Singapore, Vietnam, and Thailand during the COVID-19 pandemic from March 2020 to May 2020. Medical device and multimedia acts were identified through the Google search engine.

Inclusion criteria were full-text articles and gray materials (i.e., policy statements, advisories, blueprints, executive summaries, and circulars) related to telemedicine guidelines. No distinction was made to differentiate between advisories, guidelines, regulations, or laws. Only the first 100 Google searches were included for eligibility, as searches beyond 100 articles were repetitive and were not related to telemedicine guidelines. No language restrictions were imposed. Translations of original articles into English were included if they fulfilled the eligibility criteria. Only full-text articles were included, and duplicates were removed.

Exclusion criteria were abstracts, promotional brochures, blogs, news articles, conference proceedings, and specific telemedicine projects unrelated to telemedicine guidelines. Eligible studies were assessed for domains similar to a study published by Mars et al. (16) on WhatsApp guidelines. The domains were categorized into three main themes:

- Clinical aspects of telemedicine—definitions, clinical governance, applications, and international service.
- Ethical and legal issues—confidentiality, privacy, security, consent, identification, authentication, licensing, and cyber laws.
- Technical and operational issues—record keeping, data storage, phone stewardship, cost, billing or reimbursement, mHealth Apps, feedback, and choices offered to telemedicine users.

Articles retrieved from the literature search were screened at the title level by the first author ISM. Two reviewers (IRD and NHB) independently verified the accuracy and eligibility of the full-text articles. Any disagreement in the selection process was resolved by a consensus and consulting a third reviewer (PSR).

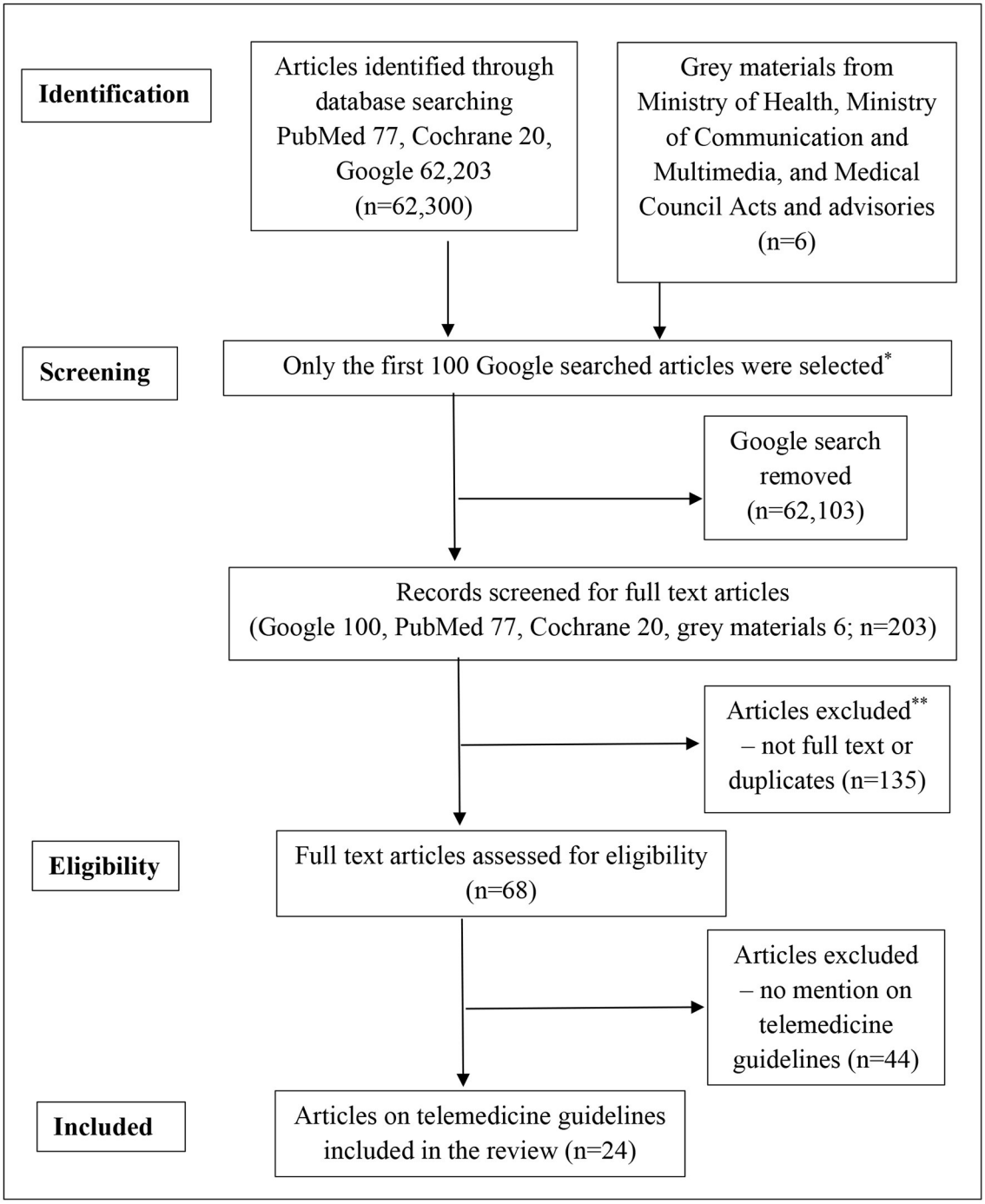

FIGURE 1 | Flowchart of article selection. *Current conventional research methodology only includes the first 100 Google findings. **Blogs, news articles, promotional brochures, conference proceedings, and telemedicine projects unrelated to telemedicine guidelines.

RESULTS

A total of 62,300 articles were identified through the search engines (Google 62,203, PubMed 77, and Cochrane 20) (see **Figure 1**). Six telemedicine and information technology laws were obtained from the Ministry of Health and Ministry of Communication and Multimedia of Malaysia and Indonesia. Searches from the Cochrane Library found no systematic reviews on telemedicine guidelines. Sixty-eight full-text articles fulfilled the inclusion criteria, but only 24 articles published from 1997 to

2020 contained some form of guidelines on telemedicine in SEA: Indonesia (nine), Malaysia (seven), Singapore (five), Thailand (two), and Vietnam (one).

Most articles were advisories (10, 17), policy statements (18–20), laws (21–26), circular (27), and blueprints (28–30) issued by the Ministry of Health (11, 20–24, 27–32) (50%) and Medical Councils (10, 18, 19) (16.7%). Five (20.8%) review articles (14, 33–36) discussed the current and future trends and best practices in telemedicine. Only Singapore (21), Malaysia (22–25), and Indonesia (26) have laws on telemedicine and the dissemination of electronic information. **Table 1** shows a list of articles on telemedicine guidelines in SEA countries. The domains contained in the telemedicine guidelines are summarized in **Table 2**.

Clinical Aspects of Telemedicine

Definitions of Telemedicine and Telehealth Products

Several terminologies were used to define telemedicine, such as "remote consultation," (18, 19) "virtual consultation," (10) "distant medicine," (27) "e-Health and digital technologies" (30), and "cybermedicine and telemedis" (33). Although most guidelines include medical activities and services involving ICT as part of telemedicine (10, 14, 17–24, 28, 29, 31–36), the latter refers to long-distance medical service in Thailand (30) and Vietnam (27).

Telehealth products may be defined as any instrument, appliance, software, or similar applications intended by the manufacturer to be used alone or in combination for the purpose of diagnosis, prevention, monitoring, treatment, or support of the anatomy or physiological process (28, 29, 32). Devices that monitor biometrics or lifestyle habits are not considered telehealth products in Singapore (32). Other SEA countries do not have clear definitions of telehealth products or the scope of its use in telemedicine services within or beyond their country.

Applications and Restrictions in Telemedicine

Almost all guidelines from SEA countries outlined the spectrum of telemedicine from real-time telehealth such as tele-consultation (10, 14, 17–20, 27, 33–36), tele-treatment (17, 34), tele-surgery (34, 35), tele-rehabilitation (34), tele-pharmacy (17, 31, 34), tele-radiology (17, 27), tele-pathology (17, 27, 34), tele-diagnostic (14, 27) to remote patient monitoring (17, 27, 34), tele-support (17), tele-coaching (34), tele-nursing (34), tele-homecare (17, 34), tele-rehabilitation (34), tele-collaboration (14, 17, 35), and tele-education (14, 17, 27, 28, 33, 34). The scope of telemedicine services depends on the existing needs and policies of the organization and medical councils. Most guidelines issued by the medical councils in Malaysia (10), Indonesia (11, 20), Singapore (17–19), and Vietnam (27) tend to regulate health-care professionals rather than the technologies, platforms, or type of telemedicine services (10). Telemedicine can only be conducted at registered health facilities in Indonesia (11, 31) and Vietnam (27). It is unclear how such rules apply to mobile applications in the respective countries. The guidelines from Singapore, Malaysia, and Thailand are less restrictive on where and how telemedicine activities can be carried out.

Tele-consultation is only permitted for patients already known to the health-care practitioners and/or as part of a continuation of care in Singapore (17–19) and Malaysia (10). New referrals, emergency cases, and invasive procedures require face-to-face consultation and physical presence in Malaysia (10) and Indonesia (11, 20). Telemedicine guidelines from Thailand and Vietnam made no mention of patient-selection, technologies, or platforms for tele-consultation.

Tele-pharmacy (e-pharmacy) is a mode of pharmacy service that utilizes technology to improve access, such as online prescription and/or counseling and dispensary *via* postal services (32). Prescriptions are transmitted electronically through a closed-loop electronic interface from the licensed practitioner to the licensed pharmacist on secured online platforms (31, 32, 36). The medicines are then delivered directly to the patients *via* postage or collected at designated pharmacies. Only Singapore and Indonesia have guidelines on electronic prescriptions, which can only be performed by licensed health-care medical practitioners and must not include narcotics and psychotropic drugs (31, 32). The telemedicine guideline from Vietnam permits a spectrum of telemedicine services, from diagnosing to prescribing appropriate treatment (27). However, it is unclear if the latter included tele-pharmacy. At present, online prescriptions other than narcotics and psychotropic drugs are only permitted as a continuation of care in Malaysia (10).

Clinical Governance and International Service

Most telemedicine guidelines have elements of clinical governance (10, 11, 17, 27, 30). Only registered health-care practitioners are allowed to practice telemedicine in their respective countries (10, 11, 17, 27, 33–36). International telemedicine service should be delivered in collaboration with the health-care provider licensed in the patient's country (10, 17, 22). The telemedicine guidelines from Singapore, Indonesia, and Vietnam have provisions for patients to receive treatment from abroad, including overseas medical facilities, agencies, organizations, and individuals related to telemedicine activities (17, 27, 31). The latter implies a spectrum of services, from referring a patient to diagnosing, imaging, operating, and prescribing appropriate treatment (27).

Ethical and Legal Aspects of Telemedicine

Ethics

Health-care practitioners must adhere to the same ethical standards and code of conduct, whether the telemedicine service is sourced locally or from abroad (10, 17, 22, 27). Distance medical advice may only be given within the scope of the specialty outlined in the practicing certificate of the provider for the advice (10, 17, 27, 36). The medical council jurisdiction of each country only applies within its country (10, 19, 20). Physicians must ensure that proper liability protection is in place to provide indemnity for malpractice (10, 19).

Legislation and Licensing of Telehealth Products

Singapore and Malaysia are the only SEA countries with separate laws to regulate telemedicine practices (21, 22) and telehealth products (23, 24, 32). The Telemedicine

TABLE 1 | Summary of telemedicine guidelines in South East Asian countries.

No.	Article Title	Author(s)	Country of origin, year	Scope/domain/element	Type of article	Main findings
1.	National Telemedicine Guidelines for Singapore	National Telemedicine Advisory Committee	Singapore, 2015	Clinical, ethical, technical, and operational aspects of telemedicine and practitioners.	Advisory guidelines	Definitions of telemedicine, consent, identification confidentiality, privacy, security, record keeping, data storage, licensing, clinical governance, ethics, legal issues, cost, user feedback, and options.
2.	Ethical code and ethical guidelines 2016 Edition	Singapore Medical Council	Singapore, 2016	Clinical, ethical, technical, and operational aspects of telemedicine and health practitioners.	Advisory guidelines	Guideline on "remote consultation" (telemedicine) for initial and continuing care consultations, confidentiality, identification, record-keeping, international service, licensing, fees, and clinical governance.
3.	Ethical code and ethical guidelines 2002	Singapore Medical Council	Singapore, 2002	Clinical, ethical, technical, and operational aspects of telemedicine and health practitioners.	Advisory guidelines	Guideline on remote initial consultations and remote consultations (telemedicine) in continuing care, confidentiality, identification, record-keeping, licensing, and clinical governance.
4.	Health care Services Act (HCSA)	Ministry of Health, Singapore	Singapore, 2021–2022	Clinical, ethical, and legal aspects of telemedicine licensing, technical, and operational standards.	Act	Licensing, ethics, quality assurance, and clinical governance of health-care service providers (Principal Officer and Clinical Governance Officer).
5.	Regulatory Guideline for Telehealth Products	Medical Devices Branch, Health Sciences Authority	Singapore, 2019	Clinical, ethical, legal, technical, and operational standards of telehealth products.	Policy statement/guidelines	Definition of telehealth, telehealth product licensing, clinical governance, and infrastructure.
6.	Layanan Telemedis di Indonesia: Keniscayaan, Risiko, dan Batasan Etika	Prawiroharjo P., Pratana P., and Librianty N.	Jakarta, Indonesia, 2019	Clinical, ethical, legal, technical, and operational aspects of telemedicine and health practitioners.	Review article	Clinical governance, ethics, confidentiality, security, privacy, legal, cost, data storage, record keeping, and infrastructure.
7.	Kebijakan Pengembangan Tele-Medisin Di Indonesia	Bernhard HS	Jakarta, Indonesia, 2015	Clinical, ethical, legal, technical, and operational aspects of telemedicine and health practitioners.	Review article	Confidentiality, record keeping, data storage, clinical governance, ethics, legal issues, human resource, infrastructure, international service, spectrum of telemedicine services, and cost.
8.	Peraturan Konsil Kedokteran Indonesia Nomor 74 Tahun 2020 Tentang Kewenangan Klinis dan Praktik Kedokteran Melalui Telemedicine Pada Masa Pandemi Corona Virus Disease 2019 (Covid-19) di Indonesia	Supriyanto B. and Ekatjahjana W. Indonesian Medical Council	Indonesia, 2020	Clinical, ethical, technical, and operational aspects of tele-consultation and tele-practice.	Advisory guidelines	Definitions, consent, clinical governance, ethics, confidentiality, record keeping, data storage in medical and health facilities (Fasyankes), imbursement, and prohibitions.

(Continued)

TABLE 1 | Continued

No.	Article Title	Author(s)	Country of origin, year	Scope/domain/element	Type of article	Main findings
9.	Permenkes No. 20 Tahun 2019 tentang Penyelenggaraan *Telemedicine* antar Fasilitas Pelayanan Kesehatan	Moeloek NF and Ekatjahjana W. Ministry of Health, Republic of Indonesia	Indonesia, 2019	Clinical, technical, and operational aspects of telemedicine services.	Advisory guidelines	List of definitions related to telemedicine, diagnostics, record keeping, infrastructure and Apps licensing, human resource, leadership, ethics, identification, consent, confidentiality, clinical governance, task of health-care facilities that provide telemedicine, cost, reimbursement, and funding regulation in Indonesia.
10.	Peraturan Badan Pengawas Obat dan Makanan Nomor 8 Tahun 2020 Tentang Pengawasan Obat dan Makanan Yang Diedarkan Secara Daring	Ministry of Health, Indonesia	Indonesia, 2020	Clinical, ethical, legal, technical, and operational aspects of tele-pharmacy.	Policy statement/guidelines	Definition, privacy, confidentiality, consent, identification, clinical governance, ICT infrastructure, ethics, legal, licensing, and mHealth.
11.	Kajian Tekno-Ekonomi pada *Telehealth* di Indonesia (*Techno-Economic Study on Telehealth in Indonesia*)	Sri A and Kautsarina	Jakarta Pusat, Indonesia, 2017	Clinical, technical, and operational aspects of telemedicine.	Review article	Capital and operational expenditures of telehealth programs, definition, infrastructure, clinical governance, record keeping, and data storage.
12.	Overview of Telemedicine Activities in Indonesia: progress and constraints	Andriyan B. S., Sastro-kusumo U., Tati L.R. et al.	Bandung, Indonesia, 2004	Clinical, technical, and operational aspects of telemedicine.	Review article	History, present, and development of telemedicine in Indonesia, international service, and parties involved in telemedicine.
13.	Surat Edaran Nomor HK.02.01/Menkes/303/2020 Tentang Penyelenggaraan Pelayanan Kesehatan Melalui Pemanfaatan Teknologi Informasi Dan Komunikasi Dalam Rangka Pengahan Penyebaran Corona Virus Disease 2019 (Covid-19)	Ministry of Health, Indonesia	Indonesia, 2020	Clinical, ethical, technical, and operational aspects of telemedicine and health practitioners.	Circular/guidelines	Definitions, clinical governance, privacy, security, record keeping, infrastructure, ethics, and cost.
14.	Law of the Republic of Indonesia Number 11 of 2008 Concerning Electronic Information and Transactions Undang-undang Republik Indonesia Nomor 11 Tahun 2008 Tentang Informasi Dan Transaksi Elektronik.	Ministry of Law and Human Rights, Indonesia	Indonesia, 2008	Legal, technical and operational aspects of information and electronic transactions.	Act	Definitions, governance, security, record keeping, storage, distribution, infrastructure, legal

(Continued)

TABLE 1 | Continued

No.	Article Title	Author(s)	Country of origin, year	Scope/domain/element	Type of article	Main findings
15.	Malaysian Medical Council Advisory on Virtual Consultation (during the Covid-19 pandemic)	Malaysian Medical Council	Malaysia, 2020	Clinical, ethical, legal, technical, and operational aspects of telemedicine and health practitioners.	Advisory guidelines	Definition of "virtual consultation" (telemedicine), ethics, patient and health-care practitioner identification, consent, ethics, clinical governance, and legal.
16.	Telemedicine Flagship Application: Malaysia's Telemedicine Blueprint Leading Healthcare into the Information Age	Ministry of Health, Malaysia	Malaysia, 1997	Clinical, legal, technical, and operational aspects of telemedicine.	Policy statement	List of definitions and applications of telemedicine, infrastructure, data storage, record-keeping, legal, and cost.
17.	HIMS Blueprint – toward excellence in Health Information Management	Health Informatics Center, Planning Division, Ministry of Health Malaysia	Malaysia, 2013	Technical and operational aspects of telemedicine (Health Information Management and Support Services) in MoH and related agencies.	Policy statement	Confidentiality and privacy, security and data protection, consent, user access, role of stakeholders, infrastructure support, health informatics standards, capacity, and capability building.
18.	Telemedicine Act 564	Ministry of Health, Malaysia	Malaysia, 1997	Clinical, ethical, legal, technical, and operational aspects of telemedicine and health practitioners.	Act	Definitions of telemedicine and health-care practitioners, confidentiality, identification, record keeping, data storage, international service, ethics, and legal issues.
19.	Medical Device Act (737) 2012	Medical Device Authority, Malaysia	Malaysia, 2012	Clinical, legal, technical, and operational aspects of medical devices.	Act	Definition and classification of medical device, therapeutic and diagnostic digital applications and data, clinical governance, licensing, maintenance, legal issues, and fees.
20.	Medical Device Authority Act (738) 2012	Medical Device Authority, Malaysia	Malaysia, 2012	Clinical, legal, technical, and operational aspects of control and regulation of all matters relating to the medical device, the industry, and its activities.	Act	Clinical governance, licensing, infrastructure, research, and training, legal and funding issues.
21.	Laws of Malaysia Act 588 Communications and Multimedia Act 1998	Ministry of Multimedia and Communication, Malaysia	Malaysia, 1998	Legal and technical aspects of information sharing on the internet.	Act	Governance, infrastructure, licensing, legal, and intellectual property.
22.	eHealth Strategy, Ministry of Public Health (2017–2026)	Ministry of Public Health, Thailand	Thailand, 2017	Clinical, technical, and operational aspects of telemedicine and health innovation.	Policy statement	Definitions and benefits of eHealth; electronic health record and eHealth uptake; ICT and telemedicine infrastructure and readiness; and 5-year eHealth action plan compliant with the digital economy.

(Continued)

TABLE 1 | Continued

No.	Article Title	Author(s)	Country of origin, year	Scope/domain/element	Type of article	Main findings
23.	Ethics, social medical and e-health in Thailand	Suttisak J.	Thailand, 2015	Clinical, ethical, legal, technical, and operational aspects of telemedicine and social media.	Literature review	Definitions, social media Apps, privacy, security, confidentiality, identification, legal, ethics, record keeping, storage, clinical governance, infrastructure.
24.	Regulating the management of Distance Medicine (Circular No. 49/2017/TT-BYT dated December 28, 2017 on telemedicine)	Ministry of Health, Vietnam	Vietnam, 2017	Clinical, ethical, legal, technical and operational aspects of distance medicine within Vietnam and Vietnamese medical facilities from abroad	Circular/ guidelines	Definition of "distant medicine" (telemedicine), confidentiality, ethics, data storage, clinical governance, licensing, infrastructure, cost, and international service. Distance medicine activities may only occur at licensed facilities; storage and compression of images must be on a 4 Mbps or faster line.

Act from Malaysia (22) focuses on regulating health-care professionals practicing telemedicine. The Healthcare Services Act of Singapore (21) is designed to ensure patient safety through proper licensing of medical institutions and professionals providing telemedicine services. Laws that apply to all telehealth products (23, 24, 32) are separate from the practice of telehealth services (21, 22) in Singapore and Malaysia. Devices that are intended to promote wellness do not fall under the purview of telehealth laws in Singapore (32). Other SEA countries (26, 27, 34, 36) do not seem to have a clear distinction between the telehealth products and/or its use in telemedicine.

Cyber laws such as the Digital Signature/Contract Act, Computer Crime Act, Multimedia Intellectual Property Act, and Electronic Government Act of Malaysia (25) and Indonesia (26) are meant to regulate ICT copyrights and to prevent dissemination of false information on the internet. Such laws may be applied in telemedicine but need to be reviewed for its relevance (28). To date, there is no transregional telemedicine treaty in the SEA region.

None of the telemedicine guidelines or cyber laws in SEA countries outlined the procedures or best practices on tele-consultations using ICT devices such as telephone consultation or smartphone applications (Apps). Tele-consultations can only be conducted by institutions registered with the Ministry of Health in Indonesia (20) and Vietnam (27). The Singapore National Telemedicine Guidelines (NTG) deemed teleconsultations *via* mHealth and Chatbots as inappropriate (17). Malaysia and Singapore are the only countries with guidelines on differences between medical advice from advice for wellness (10, 32).

Informed Consent and Options

Other than Thailand, most telemedicine guidelines contain some elements of informed consent before the commencement of telemedicine (10, 11, 17–20, 22, 27, 31). The manner of obtaining informed consent must adhere to the medical ethics of the respective medical councils (10, 11, 17, 27). Implied consent is consent that is not expressly granted by a person but perceived by the service provider that the person has agreed to the service. Explicit consent may be obtained in verbal or written formats (10). Patients should be informed of the possible intended purpose(s) on how the data will be used and the available options before proceeding with telemedicine (17). The guidelines from Malaysia and Vietnam mentioned that the provision of telemedicine is voluntary (10, 27). Patients can withdraw from receiving telemedicine at any stage (10, 17). Telemedicine limitations must be explained to the patient (10, 11, 17), as clinical assessments may be limited to audio and visual information (10, 17). In-person assessments should be arranged if telemedicine medium were inadequate (10, 11, 17).

Privacy, Confidentiality, and Data Security

Most telemedicine guidelines have policies to protect the privacy of patient information (10, 11, 17–20, 22, 27–29). However, details on data handling and stewardship, information-sharing, and record-keeping vary from one country to another. Indonesia and Vietnam only permit telemedicine to be conducted *via* internet systems at registered health facilities (11, 27) to ensure data security and confidentiality. Indonesia, Malaysia, and Thailand have policies on data management and data security using government information networks (14, 28, 30). Most guidelines state that the responsibility of data security falls on individual telemedicine providers (17, 27).

TABLE 2 | Domains contained in the telemedicine guidelines of South East Asian countries.

Domains	Singapore ($n = 5$)	Malaysia ($n = 7$)	Indonesia ($n = 9$)	Thailand ($n = 2$)	Vietnam ($n = 1$)
Clinical					
Definitions of telemedicine	Yes	Yes	Yes	Yes	Yes
Clinical governance	Yes	Yes	Yes	Yes	Yes
Restrictions	Yes	Yes	Yes	No	No
International service	Yes	Yes	Yes	No	Yes
Ethical and legal					
Medical ethics	Yes	Yes	Yes	Yes	Yes
Legislation	Yes	Yes	No	No	No
Consent from users	Yes	Yes	Yes	No	No
Confidentiality and privacy	Yes	Yes	Yes	Yes	Yes
Identification/authentication (providers, patients)	Yes	Yes	Yes	No	No
Operational and technical					
Data security and stewardship	Yes	Yes	Yes	Yes	Yes
Record keeping and data storage	Yes	Yes	Yes	Yes	Yes
Licensing of health-care practitioners	Yes	Yes	Yes	No	Yes
Licensing of health-care facilities	Yes	Yes	Yes	No	Yes
Licensing of telehealth products (mHealth, Apps)	Yes	Yes	Yes	Yes	No
Licensing of traditional and complementary medicine	No	No	Yes	No	No
ICT infrastructure	Yes	Yes	Yes	Yes	Yes
Internet speed requirement	No	No	Yes	No	Yes
Human resource	Yes	Yes	Yes	Yes	Yes
Cost of ICT infrastructure, training, human resource	Yes	Yes	Yes	Yes	Yes
Reimbursement/service fee	Yes	No	Yes	No	Yes
Feedback from users	Yes	No	No	No	No
Choices offered to users	Yes	No	No	No	No

ICT, Information and Communication Technology; EMR, electronic medical records; HIMS, Health Information Management System; mHealth, mobile health, Apps, phone applications.

Identification and Authentication

Telemedicine providers must ensure that the identities of the parties involved, place of practice, and registration status are made known to the patient and confirm the identity of the patient at each consultation (10, 17). None of the telemedicine guidelines in SEA outlined the patient-identification and authentication processes in detail.

Operational and Technical Aspects of Telemedicine

Record-Keeping and Data Storage

Telemedicine consultations and activities must be recorded, either as manual transcripts (10, 11) or electronic medical record (10, 17, 27, 28, 30, 36) by the telemedicine provider. Records should be kept at their respective facilities (11, 27) for easy retrieval (10, 17) and audit trails (17). Medical images and video footage should be stored in the database of the telemedicine provider (11, 27). The Vietnamese guideline recommends a minimum storage capacity of 10 years (27). Other SEA guidelines did not specify any minimum requirements.

Data Ownership and Management

Malaysia and Thailand have policies on data management *via* their respective Health Information Management Systems (28, 30). The responsibility of data stewardship falls on the respective telemedicine providers (11, 17, 27, 28, 30). None of the telemedicine guidelines specifically addressed the issues of data ownership, back-up, disposal, deletion, or viral attacks. Unless telemedicine is conducted *via* registered and licensed health-care facilities with secure networks (11, 27, 31), it is unclear how data ownership, privacy, and security can be regulated. Current telemedicine guidelines and cyber laws in SEA countries have not addressed cybersecurity breaches and attacks (25, 26) in detail.

Information and Communications Technology Infrastructure

ICT is a major component in telemedicine (10, 11, 14, 17, 27, 30) and may be classified into technology and equipment (14, 17, 28, 29, 32–35). ICT infrastructure must satisfy confidentiality, safety, data security (17, 27, 28), and interoperability standards for effective and efficient delivery of telemedicine services and user satisfaction (17). The NTG from Singapore is the only guideline to mention scalability, maintenance of technology, equipment calibration, end-of-life, and e-waste disposal (17). ICT equipment and technology may require upgrades and replacement to suit evolving technology and needs (17, 35).

Vietnam is the only country to state the minimum broadband speed for teleradiology consultation and tele-education, which are 4 and 2 Mbps, respectively (27). Other SEA countries did not specify any high-definition technology. Wireless local area

network, satellite technologies, and telecommunication networks are used in Indonesia, Malaysia, Thailand, and Vietnam because of its affordability and easy access in rural communities (14, 28, 34). ICT hardware and connectivity may not be available in all health-care facilities (11, 14, 33–36) due to the high cost of setting up telemedicine infrastructure (34, 37). Health-care professionals and patients use a telephone, short messaging system, multimedia messaging system, iMessage, WhatsApp, Chatbots, email (17, 34), and other audiovisual platforms with varying broadband speed (34).

Human Resources

Almost all of the telemedicine guidelines from SEA have policies on human resources to deliver telemedicine (10, 17, 21, 27, 28). Such policies should be reviewed regularly due to the evolving nature of the field (10, 11, 31). Health-care providers should possess adequate training and competency to manage patients through telemedicine (10, 17) and act within the capacity of their qualifications and medical registration (10, 11, 17–20, 27). Health facilities should provide training and technology transfer in telemedicine, which can be developed through structured on-the-job training (17) and tele-education (27, 33, 34). Organizations offering telemedicine services should have strategies to retain personnel, including reviewing compensation to ensure that it is fair and equitable (17).

Costs of Telemedicine

The costs of telemedicine depend on the country's gross domestic product and spending on eHealth (14, 28, 30, 35). Factors to consider comprise the types of telehealth programs, number of health facilities providing telemedicine services, ICT infrastructure, capital expenditure, and operational expenditure (35). Telemedicine expenditures should be incorporated into current and planned funding structures (28, 35). Opex cost is projected to peak in the fourth year of a 5-year cycle due to internet subscription, maintenance and replacement of technology and equipment, and training health-care professionals in Indonesia (35).

Other cost issues include cost–benefits of health promotion, disease prevention, and early intervention; availability and utilization of health-care services in the community; effect of telemedicine on the cost, type, size, and distribution of health-care facilities (28); and resource allocation to achieve widespread implementation of telemedicine, financing insurance products, and reimbursement linked to telemedicine (17). The costs of providing telemedicine in health facilities in Malaysia (10, 28, 29), Singapore (17), Indonesia (20, 34, 35), Thailand (30), and Vietnam (27) are borne by the respective health-care service providers.

Reimbursement and Fees

Telemedicine is provided for free in Malaysia and Thailand, as there is no billing structure at the time of writing (10, 22, 30). IT system operating costs and other extra costs serving provision of telemedicine shall be paid in accordance with regulations of the law in Vietnam (27), Indonesia (11), and Singapore (17). None of the telemedicine guidelines from SEA contained the billing structure or which health-care providers are allowed to be reimbursed for their services.

Feedback and Evaluation

The NTG from Singapore (17) is the only guideline to mention quality improvement activities, impact on cost and accessibility of care, patient outcome and satisfaction, provider satisfaction, technical quality of service, and quality of communication. Telemedicine guidelines from Malaysia (10, 22) and Indonesia (20, 33) emphasized good patient–doctor communication to avoid medicolegal consequences.

DISCUSSION

In general, most SEA countries have guidelines on telemedicine with varying degrees of breadth and depth. Most of the SEA guidelines focused on ethical and clinical aspects of telemedicine, with less emphasis on the technology or platform to deliver the service. The NTG from Singapore (17) is the most comprehensive guideline in the SEA region and comparable with other telemedicine guidelines around the world (16, 38–44). Much is needed to standardize telemedicine guidelines so that it could be applied to the local context (1). Areas that need standardization are terminologies, restrictions, applications, legislation, and billing of telemedicine. Regulations on traditional and complementary medicine (TCM) should also be included in telemedicine guidelines, given that TCM plays an integral part in the national health-care system in Asian countries (37, 45–51). Indonesia is the only SEA country to have a policy on online TCM activities (31).

Telemedicine guidelines are meant to give practical advice to medical practitioners so that telemedicine is integrated into existing health systems (39, 42–44). Some guidelines are mandatory, whereas others are only advisories and not legally binding. The Telemedicine Act 1997 of Malaysia (22) serves to regulate and control the practice of telemedicine and matters connected therewith. Any person who practices telemedicine in contravention of the Act shall be liable to an RM 500,000 fine or imprisonment for a maximum of 5 years or both. None of the other SEA countries have specific laws on telemedicine, other than regulations for the registration of medical institution (21) and/or products intended for telemedicine services (31, 32). Most cyber laws in SEA countries were designed to protect intellectual property rights and to prevent the dissemination of false or classified information in their country (25, 26). However, these guidelines did not specify the boundaries of international mHealth services (16, 22–25). It is unclear if laws such as the Personal Data Protection Act and cyber-laws in the SEA countries (25, 26) had international jurisdiction for technology breach. The lack of uniformity in laws and regulations makes it difficult to enforce legislation in malpractice across borders (39, 52, 53). There should be international collaborations to deal with transregional jurisdiction over breach of security and other cyber-crimes.

Distance is no longer a prerequisite for telemedicine (6, 10, 11, 39) but a necessity to deliver health care (54–58). Key changes were made to existing telemedicine policies globally after the

Covid-19 pandemic in 2020 (10, 11, 39, 57, 58). Telemedicine creates opportunities for international collaborations, data-sharing, and technology-transfer among health-care providers (1, 27, 41–43, 55, 56). ICT infrastructure for telemedicine has been expanded to social media (36, 39, 55, 56, 59) to cope with the dazzling speed of information-sharing and evolving technology. Issues such as privacy, confidentiality, data security, and ownership (16, 60) must be refined, particularly when it involves international data-sharing.

Network readiness index (NRI) (61) is a quantitative measurement used as a benchmark for telemedicine readiness. Countries with lower NRI scores lag in telemedicine due to limitations in ICT infrastructure and technical expertise. Population size, geographical landscape, and country income bracket may contribute to the disparities in telemedicine readiness. Singapore is a small high-income country with a population of 5.6 million (62) and ranks the second-highest NRI in 2019, after Sweden (61). Countries with lower NRI ranking, such as Indonesia and Vietnam, face more challenges to achieve high internet and smartphone penetration (63) for its 273.5 million and 97.3 million people (62), respectively. The lack of ICT infrastructure and challenging geographical landscape (14, 34) further complicate their network readiness and advancement in telemedicine.

Despite these shortcomings, most SEA countries invest in digital health solutions due to their potential in the digital economy (8, 28, 30, 34, 35, 59, 64, 65) and its usefulness during the COVID-19 pandemic (2, 6, 54–58). The lack of ICT infrastructure in most SEA countries has been overcome by using existing resources and free mHealth Apps offering affordable consultation fees (59, 65–67). Telemedicine is provided for free in public hospitals in Malaysia, Vietnam, and Thailand at the time of writing. A 15-min tele-consultation *via* mobile applications in Singapore costs between SGD12.50 (USD 8.96) to SGD25 (USD 17.92) compared with SGD13.20 (USD9.46) to SGD27 (USD19.35) for an in-person medical consultation at government-funded polyclinics (59, 66). In contrast, a 30-min teleconsultation in Indonesia may cost between 25,000 and 75,000 Rupiah (USD 1.5–USD 5.0) in Indonesia. Other than Singapore (67), most SEA countries do not have a national insurance scheme that includes telemedicine rebates or subsidies such as Medicare in Australia (43). Uniformity in telemedicine guidelines will facilitate insurers and policymakers to reimburse telemedicine services fairly within and across countries.

LIMITATIONS OF THE STUDY

This review is limited to five countries in SEA and only focused on domains mentioned in most guidelines. Future studies should include other Asian countries such as India, China, and other Association of South East Asian Nations for a more representative overview (68). A more comprehensive review of insurance schemes and billing systems across countries will need to be undertaken to reimburse telemedicine services within and beyond the country (69).

A universal and generic guideline outlining the minimum standard for telemedicine should be set by the World Health Organization to be adapted and applied to the local context. Transregional telemedicine legislation would facilitate international cooperation in the scientific, legal, and ethical aspects of telemedicine.

This review also did not include the credentialing and training of human resources in detail, such as telemedicine services other than medical teleconsultation. Further studies should focus on specific telemedicine services such as tele-therapy or tele-diagnostics and outcome measures to improve the implementation of telemedicine. The COVID-19 pandemic forced us to relook at our health-care systems and adapt to changing consumer trends and requirements. By doing so, telemedicine may no longer be an option but be the standard of care.

CONCLUSIONS

Although there can be no "one-size-fits-all" telemedicine guideline, there should be a comprehensive and universal telemedicine guideline for any country to adapt based on the local context. Details on patient-identification, data ownership, back-up, and disposal, transregional cybersecurity laws, and ways to overcome the limitations of telemedicine compared with face-to-face consultations should be outlined clearly to ensure uniformity of telemedicine service and patient safety.

AUTHOR'S NOTE

Telemedicine is an efficient and cost-effective tool to deliver acute, chronic, primary and specialty healthcare to communities. Recent policy changes during the Covid-19 pandemic have reduced barriers to telemedicine and expanded mobile health applicability, especially *in situations* where face-to-face consultation is neither safe nor practical. A universal telemedicine guideline would be useful for healthcare providers to refer to and adapt based on local context. The aim of this scoping review is to explore telemedicine guidelines in South East Asia and compare them to existing guidelines from other regions.

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All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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A Mobile Phone App-Based Tai Chi Training in Parkinson's Disease: Protocol for a Randomized Controlled Study

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Introduction: With an increasing number of China's aging population, Parkinson's disease (PD) increases year by year. Persons with PD exhibit abnormal balance functions, leading to motor skills difficulties, such as unstable walking or even falling. Therefore, activities of daily living and quality of life are affected. This study aims to explore the effectiveness of Tai Chi training based on the mobile phone app in improving the balance ability of persons with PD.

Methods and Analysis: A randomized, single-blind, parallel controlled trial will be conducted in this study. One hundred forty-four persons with PD who meet the inclusion criteria will be randomly divided into a 1:1:1 ratio: (1) control group, (2) basic experimental group (basic app with no Tai Chi training features), and (3) balanced-enhanced experimental group (basic app with Tai Chi training features). Individuals with PD will be evaluated on balance and motor function outcomes. The primary outcome measure is the limits of stability (including the maximum excursion and direction control); the secondary outcome measures include the Unified Parkinson's Disease Rating Scale III (UPDRS-III), Berg Balance Scale (BBS), Functional Reach Test (FRT), Timed Up & Go (TUG), 6-Minute Walk Test (6MWT), and 39-item Parkinson's Disease Questionnaire (PDQ-39). Each group of patients will go through an assessment at baseline, 17 and 33 weeks.

Discussion: This study will evaluate the effectiveness of the mobile phone app Tai Chi training on the balance function of persons with PD. We assume that a challenging Tai Chi project based on a mobile phone app will improve balance in the short and long term. As walking stability progresses, it is expected that daily activities and quality of life improve. These findings will be used to improve the effectiveness of future home management measures for persons with PD.

Ethics and Dissemination: This study has been approved by the ethical review committee of the Shanghai University of Sport (approval number: 102772019RT056). Informed consent will be obtained from all participants or their guardians. The authors intend to submit the study findings to peer-reviewed journals or academic conferences to be published.

Clinical Trial Registration: Chinese Clinical Trial Registry (ChiCTR2000029135).

Keywords: randomized controlled trial, Parkinson's disease, mobile phone app, Tai Chi training, balance ability

BACKGROUND

Parkinson's disease (PD), a neurodegenerative disease, is the misfolding and accumulation of α-synuclein (α-Syn) in dopamine neurons, which cannot be degraded, leading to neuronal death (1, 2). Studies have shown that PD is still an incurable progressive disease (3, 4). The primary aim of therapy is to slow PD's progress, thus improving life quality and extending lifespan (5). A multi-center PD long-term longitudinal follow-up study showed that 34% of patients had balance instability and abnormal balance reflexes within 2 years from the diagnosis of PD, Hoehn–Yahr stage III. Fifteen years later after a follow-up on surviving patients, 92% complained of abnormal balance (6). Newly diagnosed unmedicated persons with PD exhibited abnormalities of postural sway (7, 8). As the disease progresses, persons with PD will inevitably gradually develop instability of balance, and even fall, leading to fractures and disability (9). Therapies that help to improve balance function of persons with PD include drug therapy, functional rehabilitation training, and surgical treatment (10, 11). Medopa and levodopa have an excellent effect on muscle rigidity and retardation, but they cannot alleviate nor partially relieve the PD patients' balance symptoms (12, 13). Moreover, the side effects of long-term medication and medical expenditure should be considered (14, 15). Deep brain stimulation (DBS) is a surgical treatment of movement disorders, such as PD (16). However, the application of DBS is controversial (17, 18). Therefore, persons with PD urgently need a safe, effective, and operable treatment to slow the disease's progression or adjuvant drug treatment.

As one of the non-pharmacological interventions, exercise has been shown to improve gait disturbance, abnormal balance, and fall frequency to assist PD treatment (19, 20). Data suggest that intensive exercise is more effective in controlling balance and gait for PD (21). However, the prevalence of elderly persons with PD using this exercise is very low. As a traditional Chinese martial art, Tai Chi is very popular among the elderly (22). Studies have shown that Tai Chi is a moderate-intensity aerobic exercise, which positively affects fitness and balance ability and prevents falling in older people (23). Long-term Tai Chi training enhanced the balance and stability of persons with PD (24), which may be related to Tai Chi, increasing the range of motion of various joints and improving nerves' ability to control joints (25). However, the traditional Tai Chi movement is complicated and challenging to learn; hence, memory loss of persons with PD hinders training's feasibility and effectiveness. Persons with PD mainly exercise in groups, which require a large venue and a fixed time (26). Moreover, traffic problems and time schedules to reach the training site are often the key factors restricting persons with PD. With the development of telemedicine technology, various chronic diseases have achieved home monitoring and management, laying the foundation for persons with PD to achieve home rehabilitation training (27, 28).

With the combination of information technology and health care, mobile medical apps have emerged. The US Food and Drug Administration defines them as mobile apps installed on smart mobile devices to promote health and prevent diseases (29). In recent years, mobile medical apps have achieved good results in chronic disease management and have gradually become an essential tool for managing chronic disease patients (30, 31). It may be the most promising method to support the treatment of patients with chronic disease (32). Mobile health is also used in PD. For example, ParkinsonNet in the Netherlands is a professional website that connects persons with PD and doctors, equivalent to "persons with PD Facebook" (33). The remote PERFORM system for persons with PD is used for monitoring and evaluation and manages the symptoms and changes of persons with PD (34). However, few interventions based on smartphone apps have been developed to guide PD persons' home rehabilitation training in China.

An expert team composed of occupational therapists, graphic designers, and information technology experts has developed a new app called "Shoupa" focused on balance ability. The app program can be downloaded from the WeChat Mini Program or Apple Store (https://apps.apple.com/cn/app/%E5%AE%88%E5%B8%95/id1451277034?l=en). The app contains explicitly six aspects of the management of persons with PD. As far as we know, the effectiveness of this kind of mobile phone app-based Tai Chi training has not been verified in PD.

Therefore, this study aims to verify the effectiveness of the mobile phone app-based Tai Chi training in PD. For these purposes, a single-blind randomized controlled trial (RCT) will be performed. We hypothesize that app-based Tai Chi training will improve balance ability, thereby improving daily living and the quality of life of patients with PD. Tai Chi training based on a mobile app can be done at home, so persons with PD can train at any time of the day at their convenience. Consequently, this study will evaluate the efficacy of mobile phone app combined with Tai Chi interventions.

MATERIALS AND METHODS

Study Design and Setting

This study is a single-blind (evaluators), parallel, RCT. Participants will be randomly divided into a control group, a basic experimental group, and a balanced-enhanced experimental group. Assessment will be carried out by the Shanghai University of Sport assessors at baseline, 17 weeks (end of intervention), and 33 weeks (16 weeks after follow-up). The research flowchart is shown in **Figure 1**. Ethical approval has been given by the ethical review committee of the Shanghai University of Sport (approval number: 102772019RT056, trial registration in Chinese Clinical Trial Registry: ChiCTR2000029135). The study will be performed according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines (35).

Participants and Recruitment

This study will recruit 144 eligible participants from the neurology clinic of Shanghai Tongji Hospital. Eligible persons with PD must meet the following inclusion criteria. The consort diagram of participant recruitment is shown in **Table 1**. We intend to distribute leaflets in the neurology clinic, and the neurologist will introduce and publicize the content of this study. Members of the research team will register participants interested in this training program and conduct corresponding screening evaluations. After the baseline assessment, eligible participants will be randomly assigned to one of three study groups.

Inclusion Criteria

(1) Primary PD following the standard suggested by the Clinical Diagnostic Criteria for Parkinson's Disease in China (2016) (36);
(2) Age of 50–70 years;
(3) Meet the modified Hoehn–Yahr clinical grading criteria 1–2.5;
(4) In stable condition with an essential dosage of madopar; and
(5) Voluntary cooperation when training and signing the consent form.

Exclusion Criteria

(1) Secondary PD;
(2) Psychiatric conditions;
(3) Severe medical diseases, such as severe heart, liver, and kidney diseases;
(4) Speech or cognitive impairments; and
(5) No other daily exercise history, no Tai Chi, or other rehabilitation training experience.

Sample Size Calculation

Sample size calculations are based on the primary outcome measures of maximum excursion and directional control of limits of stability (LOS) measured using NeuroCom® Balance Master. Based on data provided by Li et al. (24), the primary outcome LOS was used to assess the maximum excursion and directional control in patients with PD (Cohen's $d = 0.28$, 15% improvement in maximum excursion, 12% improvement in directional control). For the current study, a similar effect size difference is anticipated between the balanced-enhanced experimental condition and the control condition. A smaller effect size difference is anticipated between the balanced-enhanced experimental condition and the basic experimental condition, hence the larger sample size. Based on sample size calculations ($\alpha = 0.05$, $\beta = 0.2$), a total sample of 144 (assuming 15% attrition) will be sufficient to detect a small effect size (Cohen's $d = 0.25$) for between-group difference on the primary outcome if one exists.

Randomization and Allocation Concealment and Blinding

Randomization will be achieved through a random sequence table generated by a computer (Excel software; Microsoft). The subject's randomization will be carried out by a researcher who will not enroll the participants, assign them to their groups, or perform outcome measurements. The researcher will conceal the distribution in an opaque envelope, which can only be opened after the subject has completed the baseline assessment. The subjects will be randomly assigned to three groups (allocation ratio 1:1:1). Only the researcher responsible for guiding the use of the app can know how the participants are allocated. The researcher responsible for the follow-up reviews will be blinded to the distribution at any time during the data collection period. Moreover, the group assignment will be blinded to the assessors and data analysts.

Intervention

The "Shoupa" app is an efficient medical and health service platform that can record patients' medications in real-time, aiming to manage PD better. The "Shoupa" app modules contain six sessions, prescription management, medication recording, effect recording, adverse report, patient's diary, and exploratory research. Persons with PD can easily submit their condition through the "Shoupa" app, and the professional triage consultant will arrange the most appropriate doctor to answer the question. In the "effect recording" section, patients can automatically generate historical reports based on the medication effect records and can conveniently customize historical reports through the date range. The "patient's diary" section provides a professional record template, and users can update their diary daily to control their physical state. The "medication recording" section provides users with convenient and intuitive medication reminders. Users can add medication records, set reminders based on prescriptions, and/or record each medication's effects. Besides, in the "exploratory research" part, the developer inserts oriented rehabilitation training videos (Tai Chi training) as needed to realize rehabilitation under the home condition. The "Shoupa" app software has been released as iPhone and Android apps.

During the recruitment process, all participants will see the registration screen of the application. However, after random assignment, participants will only be granted access to their assigned experimental group's features. To prevent interference between the control group, the basic experimental group, and the balanced-enhanced experimental group, participants will be instructed not to discuss their exercises during the experiment. A screenshot of the "Shoupa" app is shown in **Figure 2**.

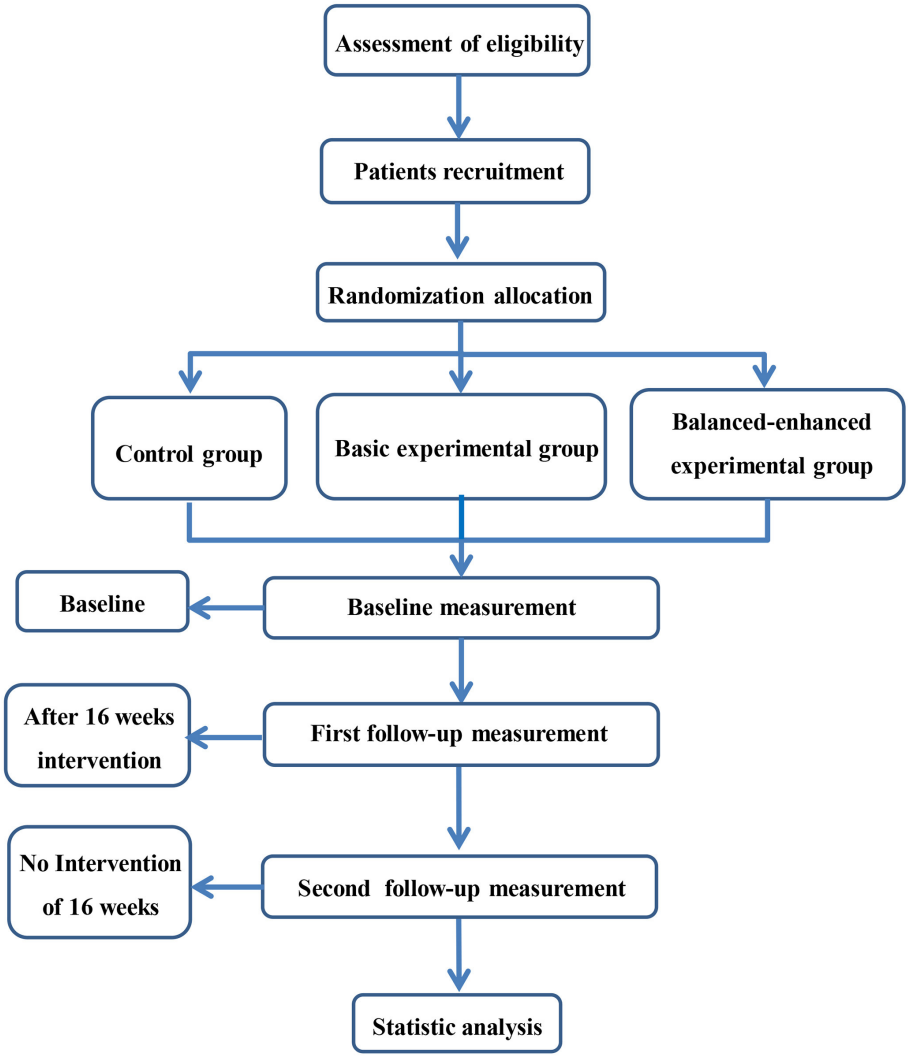

FIGURE 1 | Trail flow chart.

Control Group

Participants assigned to the control group will stay on the app's registration screen until the end of the 16-week study period. Therefore, they do not have the right to use any application functions that can help them improve their balance functions, so they will be encouraged to continue their daily activities.

Basic Experimental Group

Subjects who participate in the basic experimental group will get the self-monitoring function of using the app for daily medication management, but the "exploratory research" part of the function is prohibited. Members of the patient research team will organize persons with PD or their families to download the "Shoupa" app. Besides, the patients will perform a normal daily routine. For more information, the "Shoupa" app is presented in **Supplementary File 1**.

Balanced-Enhanced Experimental Group

Subjects participating in the balanced-enhanced experimental group are authorized to use the "exploratory research" function in addition to using the app for medication management. The "exploratory research" part is a set of simple Tai Chi training designed for persons with PD. The simple Tai Chi training is shown in **Supplementary Figure 1**. The training plan includes 60-min exercise classes, three times a week, for 16 weeks. Each session includes 40 min of the main training, 10 min of warm-up, and 10 min of finishing exercise. All exercises involve shifting the body's center of gravity (COG), as illustrated in **Supplementary File 2**. In addition to the therapist's guidance, each part of the app program contains a demo video and supporting subtitle text. The app program is connected to a website, and the clinician-side app can track the patient's training times through the website's background to monitor compliance with the plan. In other words, the "Shoupa" app records the

TABLE 1 | Schedule for data collection, the process of the assessments per visits.

Measures	Baseline (0 week)	Intervention period (1–16 weeks)	End of intervention (17 weeks)	Follow-up period (17–32 weeks)	Follow-up (33 weeks)
Participants' characteristics	√				
Limits of stability (maximum excursion and directional control)	√		√		√
UPDRS-III	√		√		√
BBS	√		√		√
FRT	√		√		√
TUG	√		√		√
6MWT	√		√		√
PDQ-39	√		√		√
Adverse experiences[a]		√		√	
Combined medication[b]		√		√	

[a] *Adverse experiences: any adverse experiences at any visit during treatment sessions and 36 weeks will be monitored. The research team will review all trial protocols, monitor patient safety, and investigate any adverse events.*

[b] *Patients will be asked whether they have used other medications during the treatment. If they have used concomitant medications, then the type and dose of medication taken by them will also be recorded in detail.*

UPDRS-III, Unified Parkinson's Disease Rating Scale III; BBS, Berg Balance Scale; FRT, Functional Reach Test; TUG, Timed Up & Go; 6MWT, 6-Minute Walk Test; PDQ-39, 39-item Parkinson's Disease Questionnaire.

training times the patient has watched the teaching course, but it is challenging to determine whether the patient is actually following the training. This requires the app to develop real-time video recording functions in future technological updates.

Every weekend during the intervention, the research team will arrange members to supervise and follow up on the participants to strengthen patients' compliance with home training. To confirm participant self-reported adherence to the study plan, patients' family members will be contacted through the phone to enquire weekly about patients' actual compliance. If participants experience dizziness, headache, or feel weak during the study, the intervention will be stopped immediately. After recovery, participants can therefore complete the interventions. If participants and their families need to consult any questions or have doubts during the study, they can always communicate with our team members. The research team will explain to the patients and their families in detail. Furthermore, the research team will count the participants who withdrew from the study and the reasons for the withdrawal.

Outcome Assessment

All participants' basic characteristics will be collected at baseline to describe the sample and study the characteristics related to the results. These baseline characteristics include age, gender, marital status, education, race/ethnicity, health status, medication use, resting blood pressure, weight (kg), and height (cm).

The experienced physical fitness assessors of the Shanghai University of Sport will assess all primary and secondary outcomes at baseline, 17 weeks (at the end of the intervention), and 33 weeks (follow-up 16 weeks later). The assessment process is shown in **Table 1**.

Primary Outcomes

The LOS is used to assess postural stability in this study. The LOS test requires each participant to intentionally displace the COG to their stability limits without losing balance. Reduced LOS can affect people's ability to complete activities of daily life that involve turning, leaning, or bending over (37) and has been associated with an increased risk of falls in several groups of patients, including the elderly and patients with neurological diseases, such as PD (38, 39).

We will assign a professional technician to perform the Balance Master® balance training tester (NeuroCom) to assess the LOS (40). These two factors will be included: (1) maximum excursion and (2) directional control.

The maximum excursion is a measure of stability. When the person tilts the body to the theoretical limit (100%) in each of the eight target directions without falling, the limit of active movement is evaluated. The average of the eight target directions (expressed as a percentage of LOS) will indicate the persons' maximum excursion during the task, and the higher percentage indicates the maximum degree of the excursion.

Directional control measures the body movement accuracy by comparing the linear distance to the desired direction (toward the target) and the persons' movement's actual path. Measurement results are expressed as a percentage (%), where a higher value indicates higher accuracy toward the intended target.

Secondary Outcomes

The Unified Parkinson's Disease Rating Scale III (UPDRS-III) commonly used in clinical practice, including 14 items, will evaluate persons' exercise capacity with PD (41); the score ranges from 0 to 56, with higher values indicating more severe movement disorders. The Berg Balance Scale (BBS), which has 14 items, will assess balance ability; the score ranges from 0

FIGURE 2 | "Shoupa" App intervention: **(A)** prescription management; **(B)** effect recording; **(C)** medication recording; **(D)** patient's diary; **(E)** exploratory research; **(F)** adverse report.

to 56, with higher values indicating better balance ability (42, 43). The BBS is used in clinical practice and shows that it is reliable, valid, and sensitive. It is currently the most widely used clinical balance scale at home and abroad (44). Functional Reach Test (FRT) assesses the maximum distance that the participant stretches forward beyond the arm length, while the patient maintains a fixed standing position during the test (45); the average of the two trials will be used; a higher score indicates better balance ability (42). Timed Up & Go (TUG) assesses the time to rise from a chair, walk 10 feet, return, and sit down (46); the lower the score, the better the mobility. The 6-Minute Walk Test (6MWT) as the name depicts assesses the distance patients can withstand walking faster within 6 min. This test can comprehensively evaluate the exercise ability of patients with chronic diseases (47). The 39-item Parkinson's Disease Questionnaire (PDQ-39) evaluates the quality of life of persons with PD. The questionnaire consists of 39 questions (eight dimensions), which reflect the quality of life of persons

with PD within the past 1 month, and higher scores indicate the worse quality of life (48).

Adverse Events

All adverse events reported during the study will be recorded on the case report form (CRF). For this trial, adverse events will be defined as any unfavorable and unexpected signs, symptoms, or diseases related to the intervention, such as falls, fractures, dizziness, and hypertension. Researchers will ask participants about the adverse events they experienced before training begins and will record all the intervention's adverse events. Participants will be phoned and asked weekly about any experienced adverse events. Subjects will also be required to report any adverse events throughout the study protocol spontaneously. A serious adverse event (SAE) will be notified to the principal investigator within 24 h. The principal investigator is responsible for managing the safety report. Any adverse events related to the intervention will be reported to the ethical review committee of the Shanghai University of Sport. Although this committee is from the same institution as the authors, the ethics committee membership is independent of the investigators. None of the investigators are members of the ethics committee.

Statistical Analysis

Data will be analyzed in an open computing environment, R language, version 3.5.2. Differences between groups of baseline variables will be tested using the chi-square test (categorical variable) and one-way analysis of variance (continuous variable). Repeated measure ANOVA will be used to compare the changes from baseline to 16 weeks among the control group, basic experimental group, and balanced-enhanced experimental group. Pairwise comparisons between the balanced-enhanced experimental group and the two other groups will be conducted only if the omnibus F-test statistics indicated that the null hypothesis should be rejected. An independent sample *t*-test (95% confidence interval) will be used to compare group means. Paired *t*-tests will be used to examine changes within the groups from baseline to 16 and 32 weeks.

Data Collection and Management

Assessments will be conducted at the Shanghai University of Sport (Shanghai, China). All assessors will receive proper instructions and guidance regarding all outcome parameters and assessments that will be taken. Research-related information, such as participant identities, data collected, and medical records, will be kept confidential. The CRF will be filled out in the paper form. The data will then be entered and stored in a password-protected electronic database. Another researcher in the team will verify data entry. All data will be monitored and reviewed by the principal investigator or research coordinators. The participants' personal information will only be accessed by the principal investigator of the research to protect patients' confidentiality. The ID list will be safely secured in a locked room for the period of the investigation and thereafter destroyed.

DISCUSSION

PD not only does reduce the patient's quality of life but also brings a heavy economic burden to society and families (49, 50). Balance dysfunction is the main reason for the increase in individuals' disability rates with PD and the decreased health-related quality of life and survival (51). Many exercise methods are designed to improve the balance ability of persons with PD (52, 53). Studies have shown that Tai Chi combines continuous and complex movements naturally, moves slowly to control multi-directional movement, and controls the COG by moving the bodyweight to focus on the control of dynamic postures (24). Tai Chi training has a beneficial effect on the persons' posture control and has attracted PD persons' attention in the community (54). Tai Chi training can effectively reduce limb stiffness in patients with mild to moderate PD, improve limb flexibility, and significantly increase lower limb strength and stride length. Furthermore, it increases walking speed, reduces the frequency of falls, and effectively improves the patient's gait and balance function (55). Henceforth, scientific physical exercise is of great benefit to persons with PD, which can help improve the balance ability, reduce the risk of falls, and improve the quality of life (52, 56, 57). However, due to the limitation of time and geographical factors, the participation of persons with PD in rehabilitation training is not high.

As smartphones and social media have been embedded in daily life, they provide a promising physical exercise platform in the home environment. Findings from the three-group RCT design, with the inclusion of a control, basic, and balanced-enhanced experimental condition, will allow for detailed examination of the efficacy of app-based PD medication management. In particular, whether the addition of Tai Chi training leads to an increase in balance ability.

Nonetheless, there are some limitations in our trial. This is a single-center study, and the number of participants in our study is not large. The multi-center study design is expected to obtain a larger sample size in the future. Moreover, the lack of patient blinding may increase bias. Participants in the control group may reduce their participation, which will increase the difficulty of recruiting subjects. The number of interventions in the balanced-enhanced experimental group will be recorded automatically by the "Shoupa" app. Conversely, the actual adherence to the intervention needs to be confirmed and followed up by weekly telephone calls. The "Shoupa" app is expected to strengthen the function of video recording to monitor the training compliance of persons with PD.

Information gained from this project has the potential to influence the clinical decisions of doctors and will provide clear evidence as to whether app-based Tai Chi training should be advocated in people with PD. In conclusion, we expect that the presented app-based Tai Chi training in the patients' home-environment will be effective in balance ability.

Ethics and Dissemination

This study has been approved by the ethical review committee of the Shanghai University of Sport (approval number:

102772019RT056). Written informed consent was obtained from the individual for the publication of any potentially identifiable images or data included in this article (specifically refers to the images in **Supplementary Figure 1**, not persons with PD). The research team will provide consultation to all participants and their families to answer any study questions. Before signing the informed consent form, the professional Tai Chi teacher will lead the interested patients to conduct two tentative training pieces to better understand this study's intervention process. After the patients and family members fully understand the study process, our team members will organize them to sign an informed consent form or withdraw from the study. Informed consent will be obtained from all participants or their guardians. The authors are inclined to submit the study findings to peer-reviewed journals or academic conferences to be published.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethical review committee of the Shanghai University of Sport. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

SG conceived the idea, supervised this study, is the guarantor, and prepared the draft manuscript. JC, QT, and PL were involved in the design. KK and YT revised the manuscript. TL, PC, and RW carried out the statistical calculation and provided funding for research. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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Adaptive Working Memory Training Can Improve Executive Functioning and Visuo-Spatial Skills in Children With Pre-term Spastic Diplegia

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Pre-term spastic diplegia (pSD) due to periventricular leukomalacia is a form of cerebral palsy in which weaknesses in executive functions are reported beyond the core visuo-spatial deficits. The study aimed at improving executive functioning and visuo-spatial skills with an evidence-based training focused on working memory in children with pSD. The intervention study followed a stepped wedge design. 19 children with pSD (11 female and 8 male; age range: 4;1–13;1 years), mild to moderate upper limb impairment and Verbal Intelligence Quotient (VIQ) >80 participated to the study. The children were trained with a home-based adaptive working memory training (CogMed®) over a 5-week period. The primary outcome measure was the CogMed Improvement index; pre- and post-test explorative neuropsychological assessment was conducted with a subset of tests from the NEPSY-II battery. Working memory training in children with pSD significantly improved trained working memory abilities (CogMed indices) as well as non-trained skills, such as visuo-spatial skills, inhibition of automatic responses and phonological processing. The results suggest that standard rehabilitation schedules for children with pSD should be integrated with trainings on executive functions.

Keywords: pre-term spastic diplegia, executive function, visuo-spatial function, neuropsychological training, cogmed working memory training

INTRODUCTION

Working memory (WM) is the ability to manipulate and update information maintained in memory for brief periods of time (1). It is important in several complex cognitive functions, such as academic learning, planning and organization of daily life activities. School-based activities, indeed, such as math and reading, depend on the ability to hold and integrate several instructions or information in mind (2–8). Working memory belongs to the family of top-down mental processes known as executive functions (EFs) (9, 10). Within a general pattern of shared but distinct EFs (11), the developmental model proposed by Diamond (7) is largely adopted to describe three main EF components: (i) inhibition, the ability to suppress automatic behaviors, memories and

thoughts in favor of goal-appropriate responses, (ii) WM, the ability to actively manipulate relevant information in memory and (iii) cognitive flexibility, the ability to switch between two or more tasks, mental sets or response rules. Although it is well-accepted that there are several processes within the EF domain (11), recent reviews of EF interventions highlight that especially WM and inhibition must be continually challenged as they are considered "tools for learning" [(12), page 363], favoring the development of other cognitive skills (6, 8, 12, 13).

Since EF deficits are typically found in children with Attention Deficit and Hyperactivity Disorder [ADHD, for a review see (14)] or traumatic brain injury (15), several studies suggest that EF impairment may be part of different neurodevelopmental disorders such as specific learning disabilities [for a meta-analysis see (16)], specific language impairment [for a review see (17)], intellectual disabilities (18, 19), autism spectrum disorders (20) and cerebral palsy, including spastic diplegia (21, 22).

Spastic diplegia is a form of cerebral palsy (CP) in which both sides of the body are involved, with a predominance to the lower limbs (23). It commonly occurs in preterm born children (pre-term spastic diplegia, pSD) and it is generally due to periventricular leukomalacia, a form of white matter brain injury typically affecting neural pathways lying close to the lateral ventricles, as the corticospinal tract and the optic radiations (24–28). Children with pSD consistently present with impaired non-verbal intelligence and visuo-perceptual and visuo-spatial abilities, while general verbal skills, as reflected by verbal Intelligence Quotient and Indices, are generally spared (26, 28–30). Beyond visuo-spatial deficits and impaired non-verbal intelligence, weak EFs have been also reported in children with pSD, such as the inability to quickly process, maintain, update and inhibit information (21, 31–36). This might be due to the involvement of white matter associative fibers altering brain structural connectivity (24, 26–28), as shown, for example, in children with unilateral periventricular leukomalacia where the altered connectivity to the anterior cingulate cortex is strongly related to EF deficits (37). In a previous study from our group (36), a multilevel organization of the neuropsychological profile in children with pSD was suggested. Beyond the common core visuo-spatial and sensory-motor deficits, when pSD was associated with thinning of the anterior/middle corpus callosum, impairments in attention and EFs seemed to act as additional factors in further affecting visuo-spatial, sensori-motor and social skills.

Despite the complex neuropsychological deficit patterns of pSD, as for other forms of CP, the majority of interventions for CP have been mainly focused on body motor functions and less is known on their effects on cognition, academic achievements and daily life skills [for a review of intervention research see (38)]. Some studies reported, in children with CP, intervention-related improvements in cognitive skills (39, 40) or in psychological well-being and social participation (39, 41–43). Evidence of training effects specifically targeting EFs is only relatively recent and scant, and has been reported for unilateral spastic CP (44, 45) but no studies to date have been performed in children with pSD.

One of the most widely used EF training programs in the scientific literature is the CogMed Working Memory Training (RoboMemo®, CogMed Cognitive Medical Systems AB, Stockholm, Sweden), an evidence-based tele-rehabilitation software, comprising several intensive visuo-spatial and verbal working memory exercises that automatically adapt the level of difficulty to the individual child's performance. In healthy adults, training effects of CogMed have been linked to significant increases of activity in parietal and pre-frontal regions on WM task-related functional Magnetic Resonance Imaging (fMRI) (46–48), supporting training-induced plasticity of the neural systems underlying WM. CogMed's home-based videogame is currently applied to different clinical populations. It has been shown to improve WM skills in children with ADHD (49–52), acquired brain injury (53) as well as in pre-term-born children. In the latter, a population at higher risk for neurodevelopmental delay and CP (54), five non-randomized trials were performed (55–59), all using the CogMed platform. Benefits of the intervention were found in trained WM tasks as well as in untrained memory tasks, in very-low and extremely-low birth weight children, especially in visuo-spatial memory (spatial span and memory for faces tasks) and in verbal short and long term memory tasks (55–57). Beyond the generalized memory improvement, the effect on untrained cognitive processes, such as auditory attention and phonological awareness found by Grunewaldt et al. (56), was not confirmed by another study, most likely due to the methodological differences between the studies (58).

Generalization effects of CogMed training are still debated as some studies have found positive effects (13, 49, 53, 60–64) while others have reported no generalized enhancements of untrained skills (59, 65). The few follow-up studies available report a partially sustained training effect after 3 and 12 months (65, 66).

The present study was aimed at determining the effects of WM training in children with pSD due to periventricular leukomalacia. As working memory represents a fundamental component of EF, it was hypothesized that improving WM may have cascade effects on the deficits classically reported in this clinical population, such as visuo-spatial or sensori-motor impairment. CogMed was chosen as it allows auto-adaptive and intensive exercises at home, reducing the number of hospital visits, which are very frequent for children with pSD. This study replicated the methods and procedures of a previous study on CogMed training on pre-term born children without neuroanatomical lesions (56). The study has been registered with ClinicalTrials.gov, number NCT02342990, on January 20, 2015.

MATERIALS AND METHODS

Participants

Sample size was calculated by expected effect size method (67) by G*Power 3 program (68). A total sample size of 19 children was selected, based on the data from 53, showing an effect size on the primary outcome measure $d = 0.8$, alpha $= 0.05$ and power $= 0.95$ for a dependent-sample t-test (critical $t = 1.73$) (69).

Nineteen children (11 females, 8 males) with pSD (mean age 7;3 years, SD: 2;4 range 4;1–13;1 years) and a mean gestational age at birth of 31 weeks (range: 28–35 weeks) were selected from a group of 30 children with a CP, recorded as spastic

diplegia according to Bax et al. (70), recruited from March 2014 to November 2015 at the Department of Developmental Neuroscience of IRCCS Fondazione Stella Maris. Children were selected according to the following inclusion criteria: (a) neuroradiological diagnosis of periventricular leukomalacia documented at brain MRI performed after age 2 years (by images or on neuroradiological reports); (b) mild to moderate functional upper limb impairment (from level I to III) at the Manual Ability Classification System- MACS (71); (c) absence of drug-resistant epilepsy; (d) absence of a psychiatric disorder diagnosis or sensory deficits that preclude testing; (e) Verbal IQ >80, as assessed in the last year prior to recruitment by WPPSI-III (72), WISC-III (73) or WISC-IV (74). The majority of children (17 out of 19) had significantly higher verbal intelligence than non-verbal. After the enrollment, the children were randomly split into two groups (Cluster A, $n = 10$ and Cluster B, $n = 9$), for sequential rollout of the training. All children were native Italian speakers of European ethnicity and followed care as usual motor rehabilitation. A subset of the children included were part of a previous study (36).

The research project was approved by the Ethical Committee of the Institute (n° 13/2013). Written consent for participation was obtained from all participants' parents who also gave informed consent to publication of results.

Motor and Visual Assessment

The Gross Motor Classification System (GMCS) (75) was used to determine gross motor skills. Children were classified in five motor levels: walk without restriction (level I); walk without assistive devices but limitation in walking outdoors (level II); walk with assistive mobility devices (level III); self-mobility with limitations (level IV); self-mobility is severely limited even with use of assistive technology (level V). Manual ability was classified according to the MACS (71). Children were classified according to five motor levels: handles objects easily and successfully (level I); handles most objects but with somewhat reduced quality and/or speed of achievement (level II); handles objects with difficulty; needs help to prepare and/or modify activities (level III); handles a limited selection of easily managed objects in adapted situations (level IV); does not handle objects and has severely limited ability to perform even simple actions (level V). Visual functions were derived on the basis of chart report data from the Vision Laboratory of our Department and were assessed for the presence of the following visual deficits: stereopsis impairment, deficits in ocular motility, visual field or visual acuity. Children were classified as follows: normal, absence of deficits; mildly impaired, one or two visual deficits; severely impaired, three or more deficits.

Motor, visual, and cognitive functions of the sample are reported in **Table 1**.

All children with pSD had more impaired lower limbs (GMFCS, classification ranging from Level I to IV) than upper (MACS, inclusion criterion). Visual functions were mildly impaired in the majority of children (14/17).

Intervention Program

CogMed Working Memory Training (RoboMemo®, CogMed Cognitive Medical Systems AB, Stockholm, Sweden) contains a variety of computerized, game-format tasks that are home-based and auto-adaptive; that is, for each task, the level of difficulty is adjusted automatically to the WM span of the child. This training is available in three on-line versions depending on the child's age. Sixteen children used the school age version (CogMed RM), while three (S3, S8, and S17 in **Table 1**) used the pre-school version (CogMed JM). Pre-school children who read letters and numbers, at a preliminary qualitative assessment, used the school-age CogMed version. CogMed RM includes 12 visuo-spatial and verbal tasks, eight tasks are provided for each training session for 45 min a day; CogMed JM consists of seven visuo-spatial and verbal tasks for 20 min a day. A training period of 5 weeks, for a total of 25 sessions, was performed by each child at home. A certified coach (MCDL) introduced the CogMed program to the child and his/her family, establishing with them reward systems, goals and treatment planning and followed the training progress weekly calling the families to give advice based on the uploaded results. After the training, two indices were automatically provided by the program: CogMed improvement index, to measure working memory improvement, and CogMed progress indicators, which assesses visuo-spatial and verbal WM span [adapted from the Adaptive Working Memory Assessment; (76)]. For a detailed description of CogMed Working Memory Training see www.cogmed.com/program.

Study Design

As shown in **Figure 1**, the Stepped Wedge randomized trial design (77) adopted, was the same design previously used by Grunewaldt et al. (56) to study the CogMed effects in a group of premature pre-school children. Thus, the children were randomly split into two groups (Cluster A, $n = 10$ and Cluster B, $n = 9$), for sequential rollout of the training. Both Clusters were assessed with neuropsychological tests from the NEPSY-II at time point T0. Then children in Cluster B immediately started CogMed training, while those in Cluster A did not receive any training in the same period. Six/seven weeks later, all children (Cluster A and B) were retested (time point T1). At T1 Cluster A started CogMed training and 6/7 weeks later was retested at time point T2.

Test-retest effect was calculated comparing performance at T0 and T1 time points in Cluster A. The training effect was evaluated comparing pre- and post- training performance at NEPSY-II in all children (both Cluster A and Cluster B), controlling training differences between Clusters.

Primary Outcome Measure

The primary outcome measure was the CogMed Improvement index provided by the program, as it is largely used in literature and is representative of the main target of the training, that is, changes in working memory span (53, 56, 78). It is calculated by subtracting the Start Index (the mean of the three best accurate trials on days 2 and 3) from the Max Index (the mean of the three best accurate trials during the training period). The mean CogMed Improvement Index for children aged 7–17 years is 27 (normal range 14–40). For further details about the

TABLE 1 | Clinical characteristics of the study group of children with pSD.

	Sex	GA	Age (y;m)	Motor function		Visual function deficit	Intelligence	
				GMFCS level	MACS level		VIQ	PIQ
Cluster A								
S1	M	28	9;0	III	II	Mild	102	85
S2	M	28	6;0	II	II	NA	88	93
S3	F	29	4;1	III	I	NA	106	76
S4	M	31	5;1	III	III	Mild	108	82
S5	F	29	5;1	IV	III	Mild	114	104
S6	F	29	7;0	II	I	Mild	94	95
S7	M	35	6;1	III	I	No	92	61
S8	F	31	5;1	II	II	No	100	82
S9	F	32	8;0	II	III	Mild	82	58
S10	M	30	8;7	II	I	Mild	112	82
Mean		***30.1***	***6;7***				***99.8***	***81.8***
SD		***2.1***	***1;7***				***10.6***	***14.3***
Cluster B								
S11	M	31	8;1	II	II	Mild	104	87
S12	F	32	9;1	III	II	Mild	102	100
S13	F	32	6;1	IV	III	Mild	100	89
S14	M	30	11;0	II	II	Mild	103	59
S15	F	32	6;0	II	II	No	100	80
S16	F	34	13;1	II	II	Mild	98	93
S17	F	32	4;1	II	II	Mild	112	91
S18	M	32	7;8	II	II	Mild	100	62
S19	F	28	9;7	III	III	Mild	99	89
Mean		***31.4***	***8;0***				***102.0***	***83.3***
SD		***1.7***	***3;0***				***4.2***	***14.0***

GA, gestational age; GMFCS, Gross-Motor Function Classification System; MACS, Manual Abilities Classification System; NA, not available; No, normal visual function; VIQ, Verbal IQ at WISC-III, WPPSI-III, or Verbal Comprehension Index at WISC-IV; PIQ, Performance IQ at WPPSI-III or Perceptual Organization Index at WISC-III or Perceptual Reasoning Index at WISC-IV.

training intervention and algorithm see CogMed JM and RM; www.cogmed.com and Klingberg et al. (79).

Explorative Outcome Measures

The CogMed progress indicators assess visuo-spatial and verbal WM span with two tests, Working Memory and Following Instructions, presented by the program at the beginning, the middle and the end of the training. The Working Memory test requires the child to identify a different shape from a set of three and remember its location; in the Following Instruction test the child listens to a set of instructions and then clicks on or drags objects seen on the screen in a specific order. Both tests scores are expressed in span scores.

The CogMed rating scale questionnaire was filled out by the parents as it is aimed at monitoring the child's behavior before and after the training period. The questionnaire collects quantitative data, expressed as raw scores, on inattention, hyperactivity and impulsivity. This questionnaire was filled only by parents of school-aged children, as provided by CogMed.

For pre- and post- neuropsychological evaluation, a subset of tests selected from the NEPSY-II battery was chosen (80), with particular attention to those subtests found impaired in a previous study in children with pSD (36). They tapped the following neuropsychological areas: executive function and attention, manual planning, visuo-spatial memory and visuo-spatial processing. Performance was expressed as raw scores, which, if not otherwise specified, were referred to response accuracy, that is the number of correct responses given for each subtest.The following subtests comprised the Executive function and attention assessment:

- Visual Attention: visual search task requiring to cross out one or two targets among a variable number of distractor stimuli;
- Auditory Attention and Response Set: sustained auditory attention task requiring to shift and update new and complex set of rules involving the inhibition of previously learned responses;
- Inhibition: task requiring to inhibit automatic responses in favor of novel responses and to switch between response types. The test is divided into three conditions: naming, inhibition, and switching, but only the inhibition condition was reported.

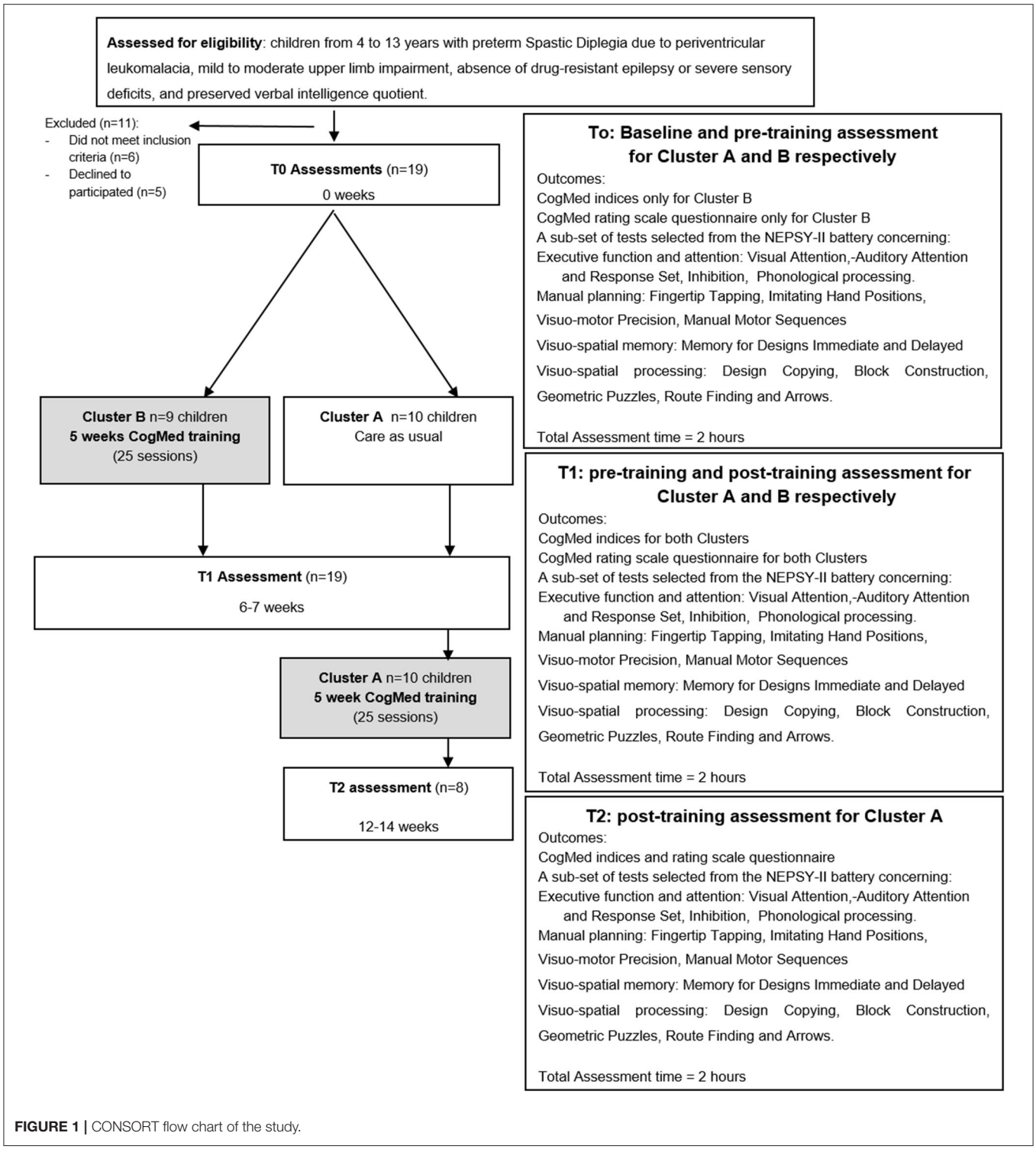

FIGURE 1 | CONSORT flow chart of the study.

Both accuracy (number of errors) and speed are recorded for each condition;

- Phonological processing: phonemic awareness task requiring to identify pictures corresponding to given word segments and to create new words by omitting or substituting a syllable or a phoneme.

For the Manual planning assessment, the following subtests were administered:

- Fingertip Tapping: tasks requiring to imitate a series of finger movements (single and sequences) with the dominant and non-dominant hand. Speed is recorded;

- Imitating Hand Positions: visuo-motor planning task requiring to imitate finger positions;
- Visuo-motor Precision: visuo-motor integration task requiring to draw a line following paths of different widths and spatial complexity. Both accuracy (number of errors) and speed are measured;
- Manual Motor Sequences: visuo-motor planning task requiring imitation of a series of hand movements.

The Visuo-spatial memory assessment comprised the following subtests:

- Memory for Designs: visuo-spatial memory task requiring to identify form and position of an abstract design on a grid with 4–10 distractors. Content (visual form recognition) and spatial (localization) scores are obtained. Memory for Design Delayed is administered 15–25 min later.

For assessing Visuo-spatial processing, the following subtests were administered:

- Design Copying: visuo-motor integration task requiring to copy geometric figures of increasing complexity;
- Block Construction: constructional praxis task requiring imitation of three-dimensional block constructions of increasing complexity starting from either a three- or a two-dimensional model;
- Geometric Puzzles: mental rotation task requiring to recognize rotated geometric shapes among a series of distractors.
- Route Finding: visual spatial relations and directionality task requiring to find the house, previously shown in a schematic map, in a larger map with other houses and streets.
- Arrows: judgement of line orientation task requiring to find the arrow(s) pointing to the center of a the target in an array of arrows arranged around the target.

Statistical Analysis

The Statistical Package for Social Sciences, version 17.0 (IBM SPSS Statistics, IBM Corporation, Armonk, NY) was used for statistical analyses.

Normality of distributions was verified by Shapiro-Wilk's test and *t*-tests or non-parametric tests were used according to normal/non-normal distributed data or to continuous/ordinal variables, respectively.

To verify the absence of clinical and performance differences at pre-training assessment and to examine test re-test effect within Cluster A, two-tailed unpaired *t*-tests were conducted on pre-training performance between Cluster A and Cluster B and two-tailed paired *t*-tests within Cluster A.

To test the training effect on primary and explorative outcome measures, Mixed ANOVAs, with Cluster as between-subject factor (A vs. B) and time as repeated factor were performed on the primary outcome measures (CogMed indices) and on the neuropsychological subtest at NEPSY-II. For multiple comparisons, the Bonferroni's correction was applied. Moreover, to determine the effect size, Cohen's d were calculated by G*Power 3 program (68).

To verify change within CogMed progress indicators and questionaires, Wilcoxon Signed Rank test were performed comparing performance across the beginning, the middle and the end of the training in the CogMed progress indicators and between pre- and post- training in the CogMed rating scale questionnaire. To describe the relationship between clinical factors and training effects, Parametric or non-parametric bi-variate correlations between clinical characteristics (VIQ, PIQ, chronological age, gestational age, GMFCS, and MACS) and CogMed Improvement index or the degree of improvement for each neuropsychological subtest were performed.

RESULTS

Neuropsychological Characteristics of the Two Clusters at Pre-training Assessment

There was no difference in chronological age ($t(17) = -1.2$, ns), gestational age ($t(17) = -1.4$, ns) and gender ($\chi^2(1) = 2.7$, ns) between the two Clusters.

At T0, no significant differences between Cluster A and Cluster B were found in verbal and non-verbal intelligence ($t(17) = -0.6$, ns; $t(17) = -0.2$, ns respectively) and in GMFCS ($\chi^2(3) = 1.6$, ns). No differences between the two Clusters were found in Start CogMed index ($t(15) = -0.3$; ns) nor in any other NEPSY-II neuropsychological subtest at pre-training assessment, except for Auditory Attention ($t(15) = -2.4$, $p < 0.05$) and Design Copy ($t(16) = -2.8$, $p < 0.05$) subtests, which, thus, were excluded from further analysis.

Training Effects on the CogMed Indices

Two children (S7 and S10), included in Cluster A, did not complete the training due to inconsistent family compliance and thus their performance was used only to verify practice test-retest effects. All the other children ($n = 17$) completed the 25-day training period and were tested at all scheduled time points.

As shown in **Table 2**, the Max Index was significantly higher than the Start Index ($F_{(1,15)} = 52.72$, $p < 0.001$), without significant Cluster's effect ($F_{(1,15)} = 0.26$, $p > 0.05$) and Cluster × Time effect ($F_{(1,15)} = 0.55$, $p < 0.05$), and a large effect size was found ($d = 1.29$). The mean Improvement Index, that did not correlate with the Start and Max indices ($r(17) = 0.4$, ns), was indeed higher (mean 25.2; SD 13.9; range between 8 and 52) than the improvement cut-off value (cut off >14).

The span scores in the Following Instruction test were significantly higher at the last session with respect to both the beginning ($Z = -2.8$; $p < 0.005$) and the middle ($Z = -2.3$, $p < 0.05$) sessions. The span scores in the Working Memory tests and the behavioral profile at the parent rating scales (filled out for the sub-sample of children who performed the school age CogMed version, $n = 14$) did not significantly change after the training (Wilcoxon signed ranks tests Z from −0.14 to −1.9, ns).

Training Effects on Neuropsychological Measures

Within Cluster A, a test-retest effect was found in Inhibition accuracy ($t(8) = 3.2$, $p < 0.05$), Finger Tapping ($t(7) = 3.1$, $p < 0.05$), Manual Motor Sequences ($t(9) = -2.6$, $p < 0.05$). Thus, in order to avoid test-retest biases, the scores of these subtests were not used to test the training effects.

TABLE 2 | CogMed working Memory indices.

	Start Index	Max Index	Improvement Index
S1	64	83	19*
S2	73	125	52*
S3	33	41	8
S4	48	63	16*
S5	54	76	22*
S6	42	78	35*
S8	39	54	14*
S9	67	80	14*
S11	61	77	16*
S12	77	101	24*
S13	66	79	12
S14	69	95	26*
S15	55	89	34*
S16	78	128	49*
S17	45	67	22*
S18	36	52	16*
S19	51	101	50*
Mean (SD)	***56.3 (14.4)***	***81.7 (23.6)***	***25.2 (13.9)***

**Significant improvement (≥1 SD from mean).*

Mean and SDs for each NEPSY-II subtest, together with the mixed ANOVAs results are presented in **Table 3**. Within the executive function and attention subtests, significant improvements were found in Inhibition speed, with a moderate effect size, and in Phonological Processing with a small effect size. At the Memory for Design subtest (immediate condition) better performance at the end of the training was found with a moderate effect size, which was non significant after Bonferroni's Correction. Among the visuo-spatial processing subtests, significant improvements were found in Block Construction with a large effect size. No signficant Cluster effect were found, and Cluster × Time effect were found only in Phonological Processing subtests, which already showed almost significant differences between Clusters ($p = 0.06$) at pre-training assessment. A small minority of the children were unable to complete the neuropsychological assessment for clinical reason. The total number of children for each subtest is indicated in **Table 3** under the heading "number of children who improved".

No significant correlations between CogMed Improvement index and verbal ($r(17) = -0.3$, ns) or non-verbal ($r(17) = 0.4$, ns) intelligence levels were found. Chronological age positively correlated with Start and Max indices ($r(17) = 0.6$, $p < 0.01$; $r(17) = 0.6$, $p < 0.01$, respectively), but not with Improvement index ($r(17) = 0.40$, ns) and no correlations were found between other clinical characteristics and CogMed indices.

Concerning the relationship between clinical characteristics and improvements in the neuropsychological profile, GMFCS level was positively correlated with the immediate Memory for design (rho(17) = 0.63, $p < 0.005$) and negatively with the Arrows (rho(14) = −0.70, $p < 0.01$) subtests. Performance IQ was positively correlated with the improvement in Inhibition Speed ($r(15) = 0.6$, $p < 0.005$) subtest, while verbal IQ was negatively correlated with Response Set ($r(8) = -0.9$, $p < 0.01$) and Imitation hand position ($r(15) = 0.6$, $p < 0.05$) subtests. No correlations were found between gestational age and MACS levels and any neuropsychological subtests.

DISCUSSION

The main finding of our study is the demonstration that, in children with pSD, a home-based and self-adaptive WM training can improve targeted WM abilities as well as other non-targeted neuropsychological functions, such as visuo-spatial processing, inhibition, and phonological processing. In agreement with previous studies conducted in different clinical populations, we showed, for the first time, a direct effect of the training on WM abilities in children with pSD. This effect translates into large and significant improvements in CogMed indices and in an more active WM task requiring to maintain and process information in memory during a fine motor task, abilities called for the Following Instruction test. Thus, children with pSD increased both memory span, that is the number of units maintained in memory, and updating, the ability to control and actively manipulate information held for a short time in memory. These results, in agreement with Diamond's recommendation of continually challenging WM (6), suggest that an intensive and automatically adjusted training may be proposed to children with pSD to improve both storage and rapid updating. No significant differences emerged between pre- and post- training assessment at the CogMed rating scale questionnaires. We can speculate that given these questionnaires were tailored for children with ADHD, they may not be sufficiently sensible to detect changing in executive function and attention difficulties associated to a neurological condition. Our findings showed a generalization of the CogMed effects to other neuropsychological processes not directly targeted by the training, some of which represent areas of weakness in children with pSD, in particular visuo-spatial and executive functions. Significant improvements, indeed, were found in visuo-spatial tasks requiring visuo-construction abilities and in executive functioning, in terms of increased speed in inhibition and in improvements in phonological WM. These results are in agreement with several studies documenting CogMed cascade effects on untrained skills in everyday functions and on the core deficit of a certain neurodevelopment disorder [for a systematic review (13, 81)].

Although these findings support, as highlighted by some authors (82), that the generalization effects of a WM training tend to mainly involve the components within the EF domain directly engaged in the training, they provide new and relevant insights for implementing cognitive rehabilitation strategies in children with pSD. In fact, WM is a transversal cognitive function, important for reasoning, comprehension and learning, which may influence cognition across-the-board and induce cascade improvements on several neuropsychological processes (83, 84). The finding of transfer effects to other impaired

TABLE 3 | Comparison between pre- and post- training performance at single subtests.

Outcome		Pre-training Mean (SD)	Post-training Mean (SD)	*F*	df	*p*	Cluster's effect (*p*)	Cluster × Time effect (*p*)	Cohen's d	*n*. of children improved
Executive function and attention	Visual Attention	4.5 (11.7)	7.5 (12.7)	3.29	1, 14	0.091	0.428	1.000	0.2	12/16
	Response Set	27.7 (8.5)	30.4 (6.4)	5.61	1, 6	0.065	0.757	0.065	0.3	4/7
	Inhibition Speed	137.6 (48.7)	122.9 (44.0)	18.08	1, 13	0.001*	0.596	0.852	0.3	13/15
	Phonological processing	33.0 (11.1)	34.3 (12.4)	13.65	1, 13	0.003*	0.124	0.004*	0.1	9/15
Visuo-spatial memory	Immediate	73.3 (37.1)	84.3 (41.0)	7.16	1, 15	0.017	0.317	0.317	0.3	11/17
	Delay	23.3 (12.2)	25.4 (14.3)	2.22	1, 13	0.160	0.103	0.103	0.2	9/15
Sensori-motor skills	Imitation hand position	10.5 (4.7)	11.5 (4.6)	2.55	1, 13	0.134	0.636	0.636	0.2	10/15
	Speed in Visuomotor precision	108.4 (48.6)	116.0 (54.1)	1.82	1, 12	0.202	0.795	0.795	0.2	4/14
	Accuracy in Visuomotor precision	59.4 (52.3)	56.8 (50.7)	0.012	1, 12	0.915	0.215	0.215	0.1	8/14
	Geometric Puzzle	17.8 (7.1)	19.7 (6.1)	9.78	1, 14	0.007	0.209	1.000	0.3	11/16
	Route Finding	3.5 (3.5)	4.7 (3.5)	6.94	1, 11	0.023	0.097	0.162	0.3	9/13
	Block Construction	8.0 (2.5)	9.8 (2.3)	28.29	1, 13	0.001*	0.863	0.112	0.7	13/15
	Arrows	14.5 (9.8)	15.5 (7.2)	1.50	1, 12	0.245	0.303	0.886	0.1	9/14

**Statistical significance after Bonferroni's Correction ($p < 0.004$) at Mixed ANOVAs for Time effect (pre- vs. post- training assessment), Cluster effect (A vs. B) and Cluster × Time effect (interaction between Cluster and Time variables). n.of children improved: the number of children with improved performance at the end of the training respect to the total number of children who had completed the subtest.*

functions is particularly important in children with pSD where the neuropsychological impairment may have a multi-level organization (36). Indeed, a training on WM may have direct effects on the EF impairment found in more than 50% of the children with pSD (36), and, at the same time, it may indirectly reduce visuo-spatial deficits, extensively documented in this clinical condition (26, 34).

In order to further understand how working memory training affects performance in children with pSD, the study analyzed whether the training effects were correlated to the clinical characteristics of the sample. No correlations were found between chronological and gestational ages, intelligence level or gross motor functioning and on the trained WM outcomes (CogMed improvement index and Following the Instructions tests). These findings are in agreement with previous evidence describing gains in WM capacity after CogMed training in different clinical populations (56, 57), and across different ages (48, 55, 63, 78, 79, 85), and support that, within a specific CP form, improvements may be found regardless of clinical variability such as different levels of motor deficit, grades of prematurity and intelligence quotients, the latter, within the normal range.

Nevertheless, improvements in the untrained tasks were found to be variably related to clinical characteristics. The gross-motor functions severity was related to the improvement in visuo-motor tasks, visuo-spatial memory and visuo-perceptual abilities: as severity of gross motor impairment increased, children showed greater gains in visuo-motor and visual memory skills but smaller improvements in a visuo-perceptual task. On the basis of these findings, although exploratory and based on a small group, one could speculate that the different generalization effects of the WM training on the neuropsychological processes found impaired in children with pSD, is related to the degree of gross motor disabilities.

Some methodological limitations of the present study should be pointed out. The data are based on a small sample of children with pSD due to periventricular leukomalacia and with average verbal intelligence, thus its findings must be confirmed in larger school-age samples, all trained with the same CogMed version. Moreover, since we used a comprehensive neuropsychological battery (NEPSY-II) to test EFs, a more fine-grained analysis of specific processes and components accounting for performance may have been highlighted, if specific EF tasks had been implemented.

In spite of these limitations, the study underlines the importance for integrating cognitive trainings focused on EF in the rehabilitation schedules of children with pSD which are most frequently focused only on motor/psychomotor interventions.

In conclusion, this study suggests that a home-based working memory training in children with pSD has a beneficial effect on trained working memory tasks as well as a generalization effect on other visuo-spatial and executive function tasks, especially for those subcomponents requiring cognitive control and updating. This study extends Grunewaldt et al.'s results in premature children showing beneficial training effects also in premature children with cerebral palsy.

Although Randomized Control Trial longitudinal studies on larger sample, with statistically more rigorous and robust comparisons of primary and secondary outcomes are needed to confirm these findings, it is suggested that a home-based WM training is an effective intervention for children with pSD which as it contributes to reducing hospital stays, already prolonged for

motor assessments and interventions, and preventing cognitive weaknesses negatively impacting educational achievement and social functions.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethical Committee of the Fondazione Stella Maris Institute. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

MD: substantial contribution to the conception and design, acquisition, analysis and interpretation of data, and drafting. CP: substantial contribution to the conception and design, critical revision for important intellectual content, analysis and interpretation of data, and drafting. PB: substantial contribution to the conception and design, critical revision for important intellectual content analysis and interpretation of data, and drafting. GS: critical revision for important intellectual content analysis, accountable for ensuring questions related to accuracy or integrity of any part of the work are appropriately investigated and resolved, and final approval. MD'O, SP, and ES: acquisition, analysis and interpretation of data. AC: substantial contribution to the conception and design and critical revision for important intellectual content. AG: critical revision for important intellectual content. GC: critical revision for important intellectual content, accountable for ensuring questions related to accuracy or integrity of any part of the work are appropriately investigated and resolved, and final approval. All authors contributed to the article and approved the submitted version.

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Social Network Structure Is Related to Functional Improvement From Home-Based Telerehabilitation After Stroke

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Objective: Telerehabilitation (TR) is now, in the context of COVID-19, more clinically relevant than ever as a major source of outpatient care. The social network of a patient is a critical yet understudied factor in the success of TR that may influence both engagement in therapy programs and post-stroke outcomes. We designed a 12-week home-based TR program for stroke patients and evaluated which social factors might be related to motor gains and reduced depressive symptoms.

Methods: Stroke patients ($n = 13$) with arm motor deficits underwent supervised home-based TR for 12 weeks with routine assessments of motor function and mood. At the 6-week midpoint, we mapped each patient's personal social network and evaluated relationships between social network metrics and functional improvements from TR. Finally, we compared social networks of TR patients with a historical cohort of 176 stroke patients who did not receive any TR to identify social network differences.

Results: Both network size and network density were related to walk time improvement ($p = 0.025$; $p = 0.003$). Social network density was related to arm motor gains ($p = 0.003$). Social network size was related to reduced depressive symptoms ($p = 0.015$). TR patient networks were larger ($p = 0.012$) and less dense ($p = 0.046$) than historical stroke control networks.

Conclusions: Social network structure is positively related to improvement in motor status and mood from TR. TR patients had larger and more open social networks than stroke patients who did not receive TR. Understanding how social networks intersect with TR outcomes is crucial to maximize effects of virtual rehabilitation.

Keywords: stroke, telerehabilitation, social networks, stroke recovery, telemedicine

INTRODUCTION

Stroke is the leading cause of acquired adult disability worldwide (1). Of the 15 million people worldwide who suffer from a stroke each year, 5 million are permanently disabled and require extensive post-stroke care. Rehabilitation, which typically includes physical, occupational, and speech therapy, can significantly improve outcomes (2). It is crucial that patients have access to rehabilitation during the first 3 months of recovery, as up to 80% of preventable stroke readmissions can be linked to health habits and post-stroke care (3, 4). However, the engagement and compliance with high-dose rehabilitation is variable and deficient in many patients with stroke (5, 6).

The coronavirus disease 2019 (COVID-19) pandemic has strained our ability to deliver critical post-stroke care. Efforts to curb COVID-19 spread have left many patients isolated from medical services they may otherwise access. These changes have especially impacted patients with stroke, many of whom are over 65 years of age and at high risk for serious illness due to COVID-19. Several countries report a decline in acute stroke admissions anywhere from 50 to 80% (7). Access to outpatient rehabilitation clinics has become significantly limited (8, 9). In addition, patients are frequently isolated from caregivers who may provide valuable support during the recovery process (10). Finally, the social isolation that many patients face during the pandemic is itself an individual risk factor for stroke recurrence (11). These barriers highlight a need for remote, accessible models of post-stroke care that account for patients' social support systems.

Telerehabilitation (TR) may address many of these limitations during the pandemic and, if integrated into routine practice, deliver valuable post-stroke care to under-resourced areas (12). In a prior study, we showed that 6 weeks of TR, targeting arm motor deficits after stroke, led to clinically significant motor gains equivalent to gains from a comparable dose of in-clinic therapy (13). We have yet to evaluate the efficacy of TR in the context of patients' social support systems, which are especially important in home-based programs that require adherence over several months. To this end, we developed a 12-week home-based TR program for stroke patients and routinely assessed motor status and mood. We then used PERSNET, a validated personal network analytic tool, to quantify the structure and composition of each patient's social network and evaluated which social factors might be important to achieve motor gains and improved mood from TR (14).

Our hypothesis, based on our prior research, was that larger network size would be associated with better stroke rehabilitation outcomes in the context of TR (15).

MATERIALS AND METHODS

Participants

All patients were enrolled at the University of California, Irvine. Protocols were approved by the University of California, Irvine's institutional review board. Subjects were recruited from the community using advertisements and mailers. All participants provided written consent for participation with the understanding that they could withdraw from the study at any time. Participants did not receive any compensation for participation. Key inclusion criteria were: age $\geq$18 years; stroke onset any time prior to study entry; arm motor deficits with an arm motor Fugl Meyer score (FM-A) of 28-66 out of 66, and if >59, must also have a Box and Blocks score on the paretic side that is >25% lower than on the non-paretic side; and minimum level of arm functioning remaining with a Box and Blocks score on the paretic arm that is $\geq$3 blocks in 60 s. Exclusion criteria were: a major, active, coexistent neurological, or psychiatric disease; a diagnosis (apart from the index stroke) that substantially affects paretic arm function; severe depression, defined as Geriatric Depression Scale Score >11/15; significant cognitive impairment, defined as Montreal Cognitive Assessment score <22/30; and deficits in communication that interfere with reasonable study participation.

Study Design

The overall study was a longitudinal examination of TR effects on recovery outcomes, with a planned nested cross-sectional analysis of social networks. This paper focused on the social network analysis, with the results of the overall study presented separately (16). Patients initially underwent an in-person assessment to measure baseline function. Baseline measures occurred over 2 visits and included arm motor Fugl-Meyer score (FM-A), leg motor Fugl-Meyer score (FM-L), Box and Blocks score (unaffected hand assessed before affected hand), gait velocity during 10-meter walk test, Geriatric Depression Scale, Montreal Cognitive Assessment, and Nottingham Sensory Assessment. These range of measures assessed upper and lower extremity sensorimotor status, gross motor function, cognitive function, and mood.

Following baseline assessment, a TR system was set up in each patient's home. The 12-week TR plan was created by a licensed occupational or physical therapist (OT/PT) following the live exam that took place at each patient's two baseline exams. During 6 training days a week, the patients completed 1 h of therapy that included functional games involving the upper and lower extremities (from 33 available), exercises (114 available), and 5 min of stroke education using a Jeopardy style game that focused on stroke prevention. Patients were allowed to use the TR system to play functional games after the day's assignments were completed or on rest days.

On selected days, training sessions included a videoconference with a licensed OT/PT 3 times/week during weeks 1–2, 2 times/week during weeks 3–4, and 1 time/week during weeks 5–12. In the videoconferences, therapists remotely assessed patients, recorded patient weight on a study provided scale, reviewed progress, provided feedback, and answered questions. Therapists regularly updated treatment plans based on feedback from the video conferences as well as data on system usage and game scores, which were collected in real-time as patients engaged with the system.

Live assessments were conducted at the clinic on week 6 and week 12. FM-A, FM-L, and 10-m walk time were reassessed at 6

Abbreviations: TR, telerehabilitation; FM-A, arm motor Fugl-Meyer score; FM-L, leg motor Fugl-Meyer score.

weeks. All baseline measures were reassessed at 12 weeks. Since TR patients were enrolled with arm motor deficits, we chose 12-week improvement in FM-A, a measure of sensorimotor impairment in the upper arm, as the primary metric for motor gains. 12-week improvement in walk time, a measure of day-to-day motor function, was our secondary metric for motor gains. 12-week improvement in Geriatric Depression score was chosen to assess changes in depressive symptoms.

Social Network Analysis

At week 6, the subjects completed the PERSNET social network survey. The PERSNET survey was an adaptation of the General Social Survey (17) and a national survey of personal networks and health (18). The research team administered the survey to the patient and recorded the patient's responses in REDCap, a web-based application for online surveys. We have demonstrated the utility of this method in health outcomes research, including studies of stroke and multiple sclerosis (19, 20).

The main sections of the survey were a name generator, name inter-relater, and name interpreter. In the name generator section, participants named people with whom they had discussed important matters, socialized, or sought support in the last 3 months. For instance, patients were asked: "From time to time, most people discuss important personal matters with other people. Looking back over the last 3 months, who are the adults with whom you discussed an important personal matter?" Patients could then choose which names to include in their network map.

In the name inter-relater section, participants determined the connections among all persons in the network and evaluated the strength of the relationship ties. Participants were asked: "Is (NAME 1) a total stranger, especially close, or in-between with (NAME 2)?" Relationship strength was quantified as 0 for total stranger, 1 for in-between, and 2 for especially close. In the name interpreter section, participants answered questions about characteristics and health habits of each individual in the network. For instance, patients were asked: "Which people in your network do you think have exercised at least 3–4 times a week in the past 3 months?" Options for each network member were "Yes, No, or Don't know." To avoid survey fatigue, name inter-relater and name interpreter data were collected for only the first 10 individuals named by the participant.

We recorded measures of each patient's personal network structure and composition. Network structure is a quantitative description of the ties in a patient's social network. For example, the number of network members is network size, and the number of ties divided by the total number of possible ties is density. Network composition is the proportion of characteristics across all persons in the network. For example, we calculate the percentage of persons who exercise more than three times per week. Network size includes all unique inputted names, whereas density, constraint, effective size, and maximum degree are calculated using tie information from the first 10 names. Size, density, and maximum degree are unweighted measures, in which we do not account for tie strength. Constraint and effective size are weighted measures in which we account for the proportional strength of the relationship between two network members. A definition of each network structure and composition metric is provided in **Table 1**.

TABLE 1 | PERSNET-derived social network metrics.

Network variable	Definition	Equation
Structural variables		
Network size	Number of individuals in the network, excluding the patient	Size $= N$ where N is the number of network members.
Network density	Number of ties divided by number of possible ties	Density $= \frac{2L}{N(N-1)}$ where L is the number of ties, and N is the number of network members.
Network constraint	The extent to which the patient is connected to network members who are connected to one another	Constraint of i's network $=$ $(p_{ij} + \sum_q p_{iq} \times p_{qj})^2$ where i is the patient, q and j are network members, p_{ij} is the proportional strength of i's relation with j, p_{iq} is the proportional strength of i's relation with q, and p_{qj} is the proportional strength of q's relation with j.
Effective size	Number of non-redundant members in the network	Effective size of i's network $=$ $\sum_j [1 - \sum_q P_{iq} \times m_{jq}], q \neq i, j$ where i is the patient, q and j are network members, and $\sum_q p_{iq} \times m_{jq}$ measures the portion of i's relationship with j that is redundant to i's relationships with other primary contacts.
Maximum degree	Highest number of ties by a network member, excluding the patient	Maximum Degree $= L_{\max}$ where $L_{\max}$ is the highest number of ties incident on a single network member.
Compositional variables		
Percentage who exercise	Ratio of network members who exercise (>3 times/week)	Ratio $= \frac{N_{yes}}{(N_{yes} + N_{no})}$ where N_{yes} is the number of nodes who share the characteristic and N_{no} is the number of nodes who do not.
Percentage who smoke	Ratio of network members who smoke (any smoking history)	
Percentage kin	Ratio of network members who are family	

Finally, we compared the network results from this cohort to 176 historical stroke controls who did not receive a post-stroke intervention, as described in a prior publication (21). Social networks were defined in the same manner using the PERSNET survey.

Statistical Analysis

We performed a series of univariate analyses using Spearman rank-order correlation to measure the association between social network characteristics and changes in motor function and mood. We used Pearson correlation to measure the association between social network characteristics and the Medical Outcomes Study Social Support Survey (MOS-SSS), an established measure of social support. We then compared social network characteristics between TR and historical stroke control patients using a Wilcoxon rank-sum test. All analyses were completed in RStudio version 1.2.1335. As this was an exploratory pilot study, we did not adjust for covariates or correct for multiple comparisons.

TABLE 2 | Baseline characteristics of the TR patient cohort.

	Overall
Number of enrolled patients	13
Sex (%)	
Female	4 (30.8)
Male	9 (69.2)
Race (%)	
White	9 (69.2)
Asian	3 (23.1)
Black or African American	1 (7.7)
Age [median (IQR)]	61 (52–65.5)
Years of education [median (IQR)]	14 (IQR=13.5–16)
Days post-stroke [median (IQR)]	129 (52–486) (range 37-1,682)
Comorbidities (%)	
Hypertension	10 (76.9)
Hypercholesterolemia	7 (53.8)
Diabetes mellitus	4 (30.8)
Atrial fibrillation	2 (15.4)
Shoulder pain present at baseline (%)	8 (61.5)
Affected side (%)	
Left	10 (76.9)
Right	3 (23.1)
Handedness (%)	
Left	3 (23.1)
Right	10 (76.9)

RESULTS

Patients in the TR cohort ($n = 13$) had a median age of 69 (IQR = 52–65.5). They were 129 (52–486) days after stroke when they enrolled. Baseline characteristics, mood, and motor function of the cohort are described in **Table 2**.

Overall, TR patients improved in stroke rehabilitation metrics over 12 weeks (**Table 3**). Specifically, median FM-A significantly improved from a baseline of 46 (42–57) to 59 (52.5–61.5) ($p = 0.0005$). Median gait velocity significantly improved from 0.94 (0.67–1.09) to 1.01 (0.83–1.21) ($p = 0.0007$). Geriatric Depression score significantly decreased over 12-weeks from 3 (1–5) to 1 (0–4) ($p = 0.05$). Details of these outcomes and other recovery markers are described separately (16).

The TR patients had a broad range of social networks, as shown in **Figure 1**. There are varying types of networks that are useful for understanding patients' social realities and planning rehabilitation. There are patients with large networks (e.g., ID10 and ID11) vs. patients with small networks (e.g., ID1 and ID2). Within the large networks of ID10 and ID11, there is a difference in density. ID10 has a star-like structure of connections usually better for informational support (e.g., hearing new ideas). ID11 has a close-knit structure usually better for instrumental support (e.g., getting a ride). The smaller networks tend to be more at-risk for reduced engagement in rehabilitation. For example, both ID1 and ID2 may require more support from external sources. ID8, ID9, and ID12 represent another pattern of network structure. Their networks have peripheral network members who are not connected to other network members. This usually occurs when the patient has made relationships in a context separate from their core relationships, such as at church or school.

In all TR patients, the mean network size was 8.3 (SD = 1.4), and mean network density was 0.74 (SD = 0.10). The mean network constraint was 0.46 (SD = 0.03), mean effective size was 3.8 (SD = 0.5), and mean maximum degree was 6.2 (SD = 1.0). In terms of composition metrics, the percentage kin was 0.49 (SD = 0.08), mean percentage who exercise was 0.51 (SD = 0.15), and mean percentage who smoke was 0.11 (SD = 0.12).

Network metrics were positively associated with improvement in stroke rehabilitation metrics. 12-week improvement in FM-A, our primary measure of motor status, was positively correlated with social network density ($r = 0.75$, $p = 0.003$). Improvement in walk time, our secondary measure of motor function, was positively correlated with social network size ($r = 0.61$, $p = 0.025$) and density ($r = 0.080$, $p = 0.003$). Additionally, 12-week improvement in Geriatric Depression score was positively correlated with network size ($r = 0.679$, $p = 0.015$; **Table 4**). Network size and density were not

TABLE 3 | Functional improvement following TR intervention.

	Baseline [median (IQR)]	**After 12 weeks of treatment [median (IQR)]**	***p*[a]**
Arm motor Fugl-Meyer score (66 max)	46 (42–57)	59 (52.5–61.5)	**$p = 0.0005$**
Gait velocity (m/s)	0.94 (0.67–1.09)	1.01 (0.83–1.21)	**$p = 0.0007$**
Geriatric depression scale score (15 max)	3 (1–5)	1 (0–4)	**$p = 0.05$**

[a]*p-values using Wilcoxon signed rank-test. Bolded values are statistically significant.*

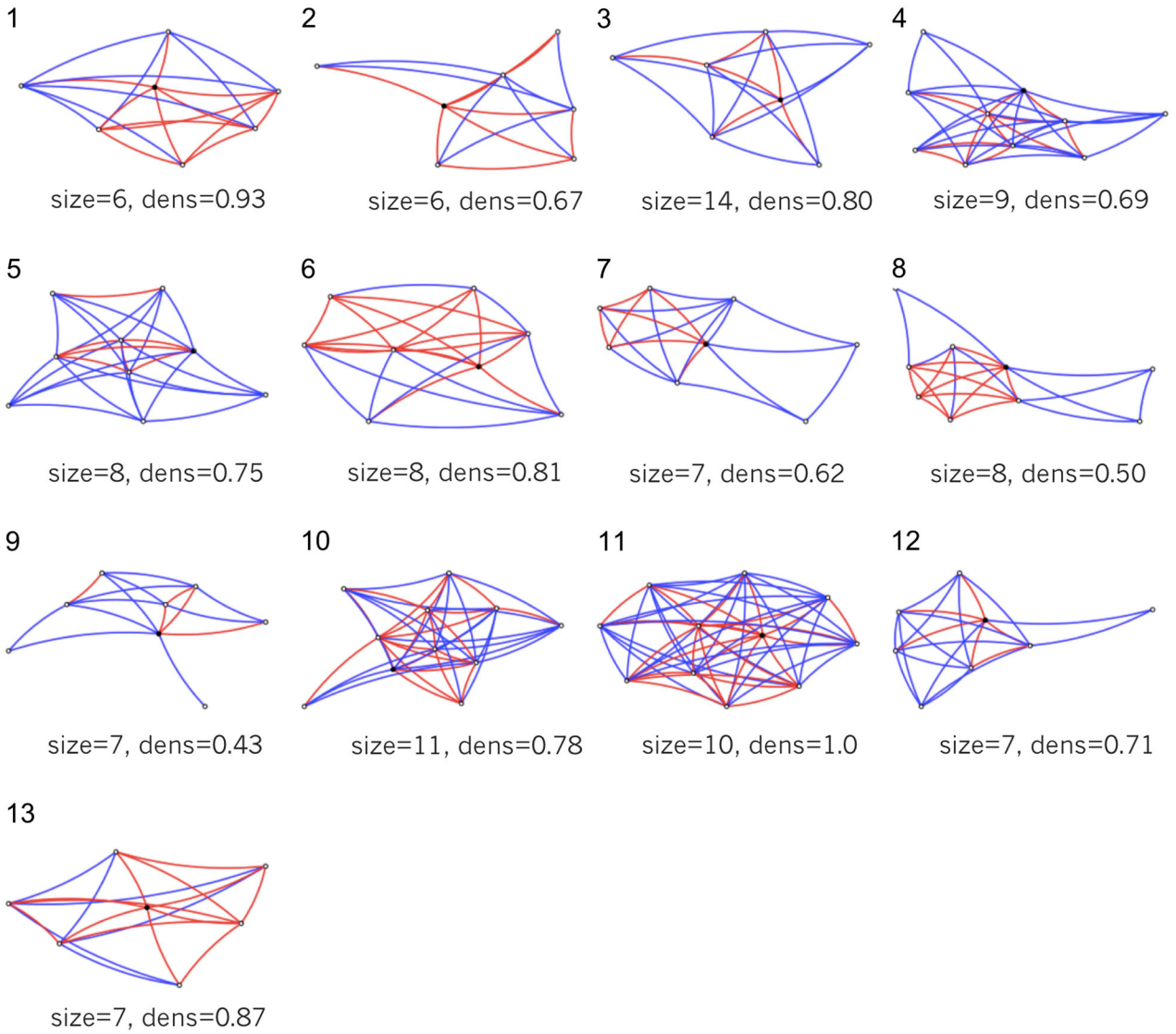

FIGURE 1 | Six-week social networks of TR patients mapped with the PERSNET algorithm. The index patient is represented by a black dot, and each of the network members is represented by an open dot. Red lines represent strong ties and blue lines represent weak ties. Graphs show only the first 10 names patients chose to include in their network maps. Patient networks reveal a broad range of social structures, from large and close-knit to moderately sparse with peripheral support nodes.

correlated within the TR cohort ($r = 0.24$, $p = 0.42$). As a validation of the social network metrics, we found that TR patients' 6-week social network size was correlated with the MOS-SSS ($r = 0.71$, $p = 0.015$), an established measure of social support. No significant correlations were observed between network size and FM-A improvement or network density and improvement in Geriatric Depression score. Network composition metrics (e.g., percentage kin) also showed no significant correlation with functional motor or mood improvement.

TR patients had larger and less dense networks compared to the networks of a historical control population of patients with stroke ($n = 172$). The control patients had a median age of 62.5 (IQR = 51–74). They had a median of 14 years of education (IQR = 12–16). 114 (66.3%) were White, 53 (30.8%) were Black or African American, 1 was Asian (0.6%), 2 were other (1.2%), and 2 were unknown or not reported (1.2%). Control patients' social networks were recorded 6 months after stroke, and full results are reported separately. Control patient networks had a mean network size of 6.7 (SD = 0.7) compared to a mean of 8.3 (SD = 1.4) in the TR cohort ($p = 0.01$). Control networks were denser than TR networks, with a mean density of 0.82 (SD = 0.05) compared to 0.74 (SD = 0.10) in TR patients ($p = 0.046$; **Table 5**). There were no significant differences in the composition, including health habits, of network members within the TR and control patient groups.

DISCUSSION

We evaluated the association of social network characteristics and stroke rehabilitation outcomes following 12 weeks of home-based TR. In this pilot study with limited sample size, we found that social network structural metrics were associated with changes in motor status and mood during TR. Patients with larger social networks showed greater functional improvement in walk time and reported greater decline in depressive symptoms following TR. Patients with denser, or more closely-knit, networks saw greater improvements in upper arm sensorimotor function and walk time. Finally, the TR cohort had larger and more open network compared to a control cohort of stroke patients who were not exposed to interventions, which suggests a relationship between network structure and participation in TR.

There are potential mechanisms in the literature as to how TR may provide social benefits for patients (22, 23). In a qualitative study of a 6-week TR program, patients reported improvements in their social and emotional well-being following the program (24). Several subjects noted that regular calls with therapists helped them feel less isolated. Thematic analysis also showed that social support and the perception of physical improvement influenced usage behavior of TR. Many patients shared that support from family members at home was a major motivator to continue with rehabilitation. These results suggest a reinforcing loop between social support and TR usage. Our work contributes to this literature by adding a quantitative study of individuals' social networks during TR and their relationship to post-stroke outcomes.

Conversely, social support might benefit TR, consistent with the growing evidence on the role of social networks in stroke

TABLE 4 | Relationships between social network metrics and improvement in stroke rehabilitation scores.

Social Network Metric	Stroke rehabilitation metric		
	12-week Arm motor Fugl-Meyer score improvement	12-week Walk time improvement	12-week Geriatric depression score improvement
Network size	$r = 0.06$	$r = 0.62$	$r = 0.68$
	$p = 0.85$	$\mathbf{p = 0.02}$	$\mathbf{p = 0.02}$
Network density	r = 0.75	$r = 0.78$	$r = 0.27$
	$\mathbf{p = 0.003}$	$\mathbf{p = 0.003}$	$p = 0.39$
Network constraint	$r = 0.03$	$r = -0.14$	$r = 0.22$
	$p = 0.92$	$p = 0.66$	$p = 0.50$
Effective size	$r = -0.57$	$r = -0.46$	$r = 0.06$
	$\mathbf{p = 0.04}$	$p = 0.11$	$p = 0.86$
Maximum degree	$r = 0.19$	$r = 0.58$	$r = -0.42$
	$p = 0.53$	$\mathbf{p = 0.04}$	$p = 0.18$
Percentage kin	$r = 0.17$	$r = 0.05$	$r = 0.31$
	$p = 0.57$	$p = 0.87$	$p = 0.32$
Percentage who exercise	$r = -0.42$	$r = 0.03$	$r = -0.33$
	$p = 0.15$	$p = 0.91$	$p = 0.30$
Percentage who smoke	$r = 0.14$	$r = 0.01$	$r = -0.06$
	$p = 0.64$	$p = 0.97$	$p = 0.85$

p-values using Spearman rank-order correlation. Bolded values are statistically significant.

TABLE 5 | Comparison of TR and control patient social networks.

	TR cohort ($n = 13$) [mean (±SD)]	Control cohort ($n = 176$) [mean (±SD)]	p^a
Network size	8.3 (7.0–9.7)	6.7 (6.0–7.4)	**0.01**
Network Density	0.74 (0.64–0.83)	0.82 (0.78–0.85)	**0.05**
Network Constraint	0.46 (0.42–0.49)	0.58 (0.54–0.61)	0.07
Effective size	3.8 (3.4–4.3)	2.9 (2.6–3.2)	**0.005**
Maximum degree	6.2 (5.2–7.1)	4.8 (4.3–5.2)	**0.04**
Percentage who exercise	0.51 (0.35–0.67)	0.44 (0.38–0.49)	0.41
Percentage who smoke	0.11 (−0.06–0.27)	0.17 (0.13–0.21)	0.15
Percentage kin	0.49 (0.41–0.57)	0.61 (0.56–0.67)	0.10

[a]*p-values using Wilcoxon signed rank-test. Bolded values are statistically significant.*

recovery. Patients often experience a contraction of social networks following stroke as they may lose contact with friends, attend fewer group events, and avoid social activities (25). This network contraction can worsen disability, as social isolation has been associated with poorer post-stroke physical outcomes and increased risk of depression 12 months following stroke. Conversely, high levels of social support are associated with faster and more extensive recovery of functional status after stroke (26). The role of social networks in recovery must be incorporated into post-stroke rehabilitation programs in order to address the compounding effects of engagement and social isolation on outcomes.

The strength of this study is that it examines the social networks of patients as a novel cofactor in their response to a novel TR intervention. The unique design of the TR program integrates physical exercises, education, and longitudinal interaction with a therapist. Additionally, the use of a retrospective control group allows for comparisons of network structure and composition between patients with stroke who did and did not undergo TR intervention. In the broader context of telemedicine and the COVID-19 pandemic, this study offers clinically relevant insights into care delivery, social support, and patient outcomes.

There are limitations to this study. The PERSNET survey requires cognitive and linguistic capabilities which may have influenced the inclusion of patients in the TR program. The different sizes of the TR and control group cohorts may have influenced estimates of social metrics within each group. Due to the limited sample size, we could not use multivariable regression to measure the effect of confounding variables in each observed relationship. Also, due to the exploratory nature of this study, we did not correct for multiple comparisons. It would be useful to repeat this study with a larger cohort of patients with diverse stroke severity to identify confounders and understand the range of network structures with which the observed relationships may hold. Moreover, our analyses rely on a single snapshot of each patient's social network over longitudinal change.

To begin to parse social processes influencing TR performance, baseline, 6- and 12-week PERSNET assessments could capture how these networks may change over the course of TR. These additional time points would allow for greater understanding of directionality of the effects. Supplementation with standardized doses of social interaction during the initial weeks of the study could help us better understand causal relationships between network structure, social interaction, and functional improvements from TR. Finally, future interventions could include approaches to increase social interactions for TR patients with smaller or sparse social networks. TR interventions could incorporate social games where patients engage with each other or a therapist. TR may also involve collaborative exercises that require patients to reach out to weak ties and form new social connections.

In summary, we observe preliminary relationships between network structure, motor gains, and mood improvement during TR. Our analyses suggest that the health of patients' social networks may be an important factor in their interaction with home-based TR systems. During the COVID-19 crisis, and as we transition toward virtual models of care, it will be important to study interactions among telerehabilitation design, patient adherence, and social support to improve outcomes from remotely delivered therapies.

DATA AVAILABILITY STATEMENT

The original contributions generated in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board (IRB) of the University of California, Irvine. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SC, AD, AP, and SR contributed to concept design, data collection, and writing of the manuscript. All authors participated in data analysis and revision.

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A Feasibility Study of Expanded Home-Based Telerehabilitation After Stroke

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Introduction: High doses of activity-based rehabilitation therapy improve outcomes after stroke, but many patients do not receive this for various reasons such as poor access, transportation difficulties, and low compliance. Home-based telerehabilitation (TR) can address these issues. The current study evaluated the feasibility of an expanded TR program.

Methods: Under the supervision of a licensed therapist, adults with stroke and limb weakness received home-based TR (1 h/day, 6 days/week) delivered using games and exercises. New features examined include extending therapy to 12 weeks duration, treating both arm and leg motor deficits, patient assessments performed with no therapist supervision, adding sensors to real objects, ingesting a daily experimental (placebo) pill, and generating automated actionable reports.

Results: Enrollees ($n = 13$) were median age 61 (IQR 52–65.5), and 129 (52–486) days post-stroke. Patients initiated therapy on 79.9% of assigned days and completed therapy on 65.7% of days; median therapy dose was 50.4 (33.3–56.7) h. Non-compliance doubled during weeks 7–12. Modified Rankin scores improved in 6/13 patients, 3 of whom were >3 months post-stroke. Fugl-Meyer motor scores increased by 6 (2.5–12.5) points in the arm and 1 (−0.5 to 5) point in the leg. Assessments spanning numerous dimensions of stroke outcomes were successfully implemented; some, including a weekly measure that documented a decline in fatigue ($p = 0.004$), were successfully scored without therapist supervision. Using data from an attached sensor, real objects could be used to drive game play. The experimental pill was taken on 90.9% of therapy days. Automatic actionable reports reliably notified study personnel when critical values were reached.

Conclusions: Several new features performed well, and useful insights were obtained for those that did not. A home-based telehealth system supports a holistic approach to

rehabilitation care, including intensive rehabilitation therapy, secondary stroke prevention, screening for complications of stroke, and daily ingestion of a pill. This feasibility study informs future efforts to expand stroke TR.

Clinical Trial Registration: Clinicaltrials.gov, # NCT03460587.

Keywords: stroke, telehealth, recovery, rehabilitation, holistic

INTRODUCTION

Stroke is perennially among the leading causes of human disability (1, 2) and the leading neurological cause of lost disability-adjusted life years (3). The number of affected people has doubled over the past two decades (4), partly because of the aging population (5) and partly because advances in stroke medicine have increased the fraction of patients surviving acute stroke (6). Motor deficits, present in >80% of patients with stroke acutely, are a major contributor to this disability. Few patients recover completely, with 55–75% having enduring motor deficits (7, 8). At 6 months post-stroke, 65% of patients are unable to incorporate the paretic hand effectively into daily activities (9). Persistent arm impairment is linked with greater activity limitations, higher participation restrictions, poorer quality of life, and reduced well-being (10–12).

There is strong evidence that higher doses of rehabilitation therapy are associated with greater behavioral gains, especially for paretic arm function after stroke (13–18), even with variability in treatment content and definition of dose (19). This remains true when higher therapy doses are delivered in the home (14, 20). However, patients generally do not receive high doses of rehabilitation therapies, due to cost, traveling difficulties, and regional shortages of rehabilitation providers–factors that are exacerbated in the COVID-19 era. Quality of rehabilitation therapy is also important and can increase the extent to which clinical neuroplasticity is harnessed (21): effects are higher when therapy is challenging, motivating, and engaging (22–25).

Telehealth might be able to help by increasing access to high quality therapy (26). Telerehabilitation (TR) has been defined as the delivery of rehabilitation services via communication technologies and encompasses a range of rehabilitation and habilitation services that include evaluation, assessment, monitoring, prevention, intervention, supervision, education, consultation and coaching (27). This is similar to the holistic framework outlined by Demiris et al. (28), who suggested that home-based post-stroke TR should include support that spans an array of medical, mental health, and social services. Compared to traditional in-clinic therapy, TR uses the same principles of individualized care by a licensed therapist. This telehealth approach provides enhanced options compared to delivery of rehabilitation services using a brick-and-mortar approach (29–33), potentially decreasing transportation needs for patients with functional limitations, boosting physical activity, and expanding access to care.

Telehealth can also help by increasing motivation and compliance. The technological underpinnings of TR can facilitate a personalized approach to upper extremity (UE) motor rehabilitation (34). Telehealth can deliver therapy in the form of games, an approach known to promote patient participation in health care (35–39). Games motivate patients to engage in enjoyable play behavior that involves therapeutically relevant movements (40, 41), which is important because patient compliance with stroke rehabilitation is often limited (42–44).

The overall experience with motor TR after stroke is mixed. While one review found that all 18 studies of post-stroke motor TR improved disability (32), a recent meta-analysis concluded that drawing general conclusions about the effects of stroke TR is difficult, as interventions and comparators varied greatly across studies (45). We have completed three trials of TR targeting arm motor deficits after stroke. The first was a pilot study (46) that provided 12 patients with chronic stroke with 4 weeks of home-based, therapist-supervised TR. Findings included that patients were highly compliant (97.9% of assigned days), videoconferences supported regular communication between the patient at home and therapists in the clinic, arm motor status improved significantly based on the UE Fugl-Meyer (UE-FM) motor scale, and no computer skills were needed, as computer literacy was not related to usage or treatment gains. With 60 min/day of TR, patients averaged 879 arm repetitions/day. A second study found that eight sessions of visuomotor training in the home improved visuomotor tracking by the UE (47).

More recently we led an 11-site, randomized, assessor-blind trial of TR (48). A total of 124 patients with stroke were randomized to receive 36 sessions of 70-min duration, either in-clinic or in the home via TR. In the 62 patients randomized to TR, UE-FM scores increased by 7.9 ± 6.7 points, and TR was found to be non-inferior to in-clinic therapy. Motor gains remained significant when patients enrolled >90 days post-stroke were examined separately. Gains were also significant when examining change in Box & Blocks score, a measure of arm function (activities limitation). In a separate manuscript under review, we found that 39.5% of patients randomized to TR and enrolled >90 days post-stroke showed reduced global disability (improved mRS score); in contrast, natural history data indicate that mRS scores generally plateau by day 90 (49, 50), suggesting that TR benefits might generalize to improved global functional outcomes.

The purpose of the current study was to evaluate the feasibility of several expansions to our prior TR program, in two main ways, treatment and assessment. Treatment topics were extension of daily TR from 6 to 12 weeks; incorporation of therapy targeting the lower extremity (LE), in addition to UE therapy; incorporation of augmented reality (AR) into this TR system; introduction of games that use a real object to train instrumental activities of daily living (iADLs); and addition of a daily study

TABLE 1 | Entry criteria.

Inclusion criteria
1. Age ≥18 years at the time of randomization
2. Stroke that is radiologically verified, with any time of stroke onset prior to randomization
3. Upper extremity motor Fugl Meyer (UE-FM) score of 28–66 out of 66; to insure some deficit is present, if UE-FM > 59, must also have Box & Blocks (B&B) score on affected side >25% lower than on non-affected side
4. Box & Block Test score with affected arm is at least 3 blocks in 60 s at the first visit
5. Informed consent and behavioral contract signed by the subject
Exclusion criteria
1. A major, active, coexistent neurological or psychiatric disease, including alcoholism or dementia
2. A diagnosis (apart from the index stroke) that substantially affects paretic arm function
3. A major medical disorder that substantially reduces the likelihood that a subject will be able to comply with all study procedures
4. Severe depression, defined as Geriatric Depression Scale Score > 11 out of 15
5. Significant cognitive impairment, defined as Montreal Cognitive Assessment score < 22; this can be waived at the discretion of the study PI, e.g., for aphasia
6. Deficits in communication that interfere with reasonable study participation
7. Lacking visual acuity, with or without corrective lens, of 20/40 or better in at least one eye
8. Life expectancy < 6 months
9. Receipt of Botox to arms, legs, or trunk in the preceding 6 months, or expectation that Botox will be administered to the arm, leg, or trunk prior to completion of participation in this study
10. Unable to successfully perform all 3 of the rehabilitation exercise test examples
11. Unable or unwilling to perform study procedures/therapy, or expectation of non-compliance with study procedures/therapy, or expectation that subject will be unable to participate in study visits
12. Concurrent enrollment in another investigational study
13. Subject does not speak sufficient English to comply with study procedures
14. Expectation that subject will not have a single domicile address during the 12 weeks of therapy, within 75 miles of the central study site

pill to be taken at the start of TR, a feature that might improve secondary stroke prevention and also might facilitate clinical trials of restorative therapies that are administered in pill form. Assessment topics included addition of tests performed by the patient using the TR system independently, with no therapist present; validation of telehealth screening for depression and aphasia; and generation of actionable email reports to clinicians whenever a critical finding occurred. The feasibility of each of these expansions was examined.

METHODS

Study Overview

In this prospective, single-group, therapeutic feasibility trial, patients underwent live assessment at the UC Irvine clinic twice at baseline, after which a telehealth system was delivered to the patient's home. Patients then received 12 weeks of TR therapy, 6 days/week, with a live clinic assessment at the end of week 6 and week 12. Patients were free to call the lab with questions. This study was approved by the UC Irvine IRB, and was registered as clinicaltrials.gov ID # NCT03460587.

Participants

Patients were recruited from the community through local advertisements. In sum, enrollees were adults with arm paresis due to stroke and no limiting cognitive deficits. Full entry criteria appear in **Table 1**. Patients signed informed consent (no surrogate consent) and were evaluated for eligibility at the first two visits.

Study Intervention

After all eligibility criteria were confirmed, the patient signed a behavioral contract (51) that listed a personal treatment goal and the time when therapy would begin each day. An initial treatment plan was created by a licensed occupational therapist (OT) or physical therapist (PT), standardized by use of an algorithm that uses the 33 UE-FM sub-scores to identify the three greatest UE impairments. The algorithm suggests games and exercises that are matched to these three impairments and so calibrates initial TR games and exercises to each patient's impairment level.

Patients were provided 72 treatment sessions, 6/week for 12 weeks. Each session was 60 min in duration and consisted of least 15 min of functional games, at least 15 min of exercises, and 5 min of stroke education using a Jeopardy style game.

There were 12 input devices used by patients to interact with the TR system: a PlayStation Eye camera, motion game controller (PlayStation Move, Sony; Tokyo, Japan), joystick, small buttons (10), large buttons (4), toy pistol holding a Wii remote (Nintendo; Kyoto, Japan) with corresponding IR sensor bar, trackpad (Logitech; Newark, CA), grip force cylinder, pinch force cube, rotating shuttle wheel (Powermate, Griffin Technology; Nashville, TN), steering wheel with gas/brake, and a 9-DOF IMU containing a 3-axis accelerometer, gyroscope, and magnetometer.

A total of 114 exercises were available, targeting UE, LE, and trunk. Each was 1–5 min long and consisted of a video showing the assigned movement. Patients were instructed to move as in the video. Therapists had the option to incorporate standard equipment (e.g., resistance bands; Theraband; Akron OH) provided to patients at the time the TR system was delivered to the home, to be used while watching the exercise videos.

A total of 33 functional games were also available, each 1–5 min long. These stress motor control features, e.g., varying movement speed, range of motion, target size, extent of visuomotor tracking, or level of cognitive demand. Game features were selected and adjusted by the therapist. For example, during the whack-a-mole game, higher difficulty level means a broader area where targets can appear on the tabletop and less time to successfully hit the target. Therapists also select which input device the patient will use for game play, based on UE status, e.g., the flappy-bird game can be played using the grip force cylinder, pinch force cube, or trackpad.

Therapists also decided whether five photographs would be taken at random time points during a given game, to gain insights into how the patient was playing the game. After the day's 1-h of assignments were completed, patients were allowed to free play, i.e., to use the system to play functional games *ad libitum*.

Stroke education targeted five categories (Stroke Risk Factors, Stroke Prevention, Effects of Stroke, Diet, and Exercise) focused on secondary prevention. Patients made arm movements to enter

their answers to multiple-choice questions, delivered via a video Jeopardy game format [an approach known to foster learning (52, 53)], and then received feedback on their answers.

To build each day's treatment session, therapists used a graphical interface to drag treatment elements into a 60-min planner for each day's session; they then adjusted the challenge level (games) and the duration (games and exercises), and selected which input device would be used to drive gameplay (games). The daily treatment plan was regularly updated by a therapist based on findings from videoconferences and from review of TR-based data. Four types of TR-based patient data were automatically transmitted from home to lab, in real time: system usage (time TR was used), patient performance (game scores), behavioral status (assessment scores), and photographs (during games and pill consumption).

Patients had 18 HIPAA-compliant videoconferences (VSee software; VSee; Sunnyvale, CA) with a licensed therapist: three times/week during weeks 1–2, two times/week during weeks 3–4, and one time/week during weeks 5–12. During videoconferences, questions were answered, feedback was provided, progress was reviewed, and on some days remote assessments were made.

During the 30 min prior to the TR session, the computer alerted the subject that the start time was coming soon. The subject hit a large tabletop button to begin the day's session and to start subsequent games/exercises after each one is completed. In this way, patients could take a break between games/exercises. Unsupervised sessions had the same treatment content as supervised sessions, but no therapist contact.

Novel TR Features Evaluated

Key novel features added to the TR system and evaluated included the following:

(1) Lower extremity games and exercises: Our prior three TR studies (46–48) were focused exclusively on UE therapy. Here we also targeted the paretic LE, introducing LE exercise videos, LE driving games, and the AR "virtual varmint" game. In the driving games, patients used a steering wheel and gas/brake pedals to navigate a virtual terrain.

(2) Augmented reality (AR) gaming: With an AR-based approach, subjects interact in the real-world workspace with virtual computer-generated objects (47, 54, 55). This was used in the Virtual Varmint game, where subjects looked at a tabletop monitor that showed a real-time video display of their paretic foot; a virtual gopher was projected into this display, and when the subject's foot overlapped with the gopher, points were earned. A camera was placed under the table and pointed at the paretic foot. The TR computer displayed camera output on the tabletop monitor along with a computer-generated varmint (a gopher). Patients looking at the tabletop monitor thus used real-time images of their foot movements to manipulate a virtual varmint.

(3) Use of real objects to drive gameplay targeting Instrumental Activities of Daily Living (iADL): The TR accelerometer had a magnet and was attached to a lemonade pitcher by the patient prior to starting the game. Accelerometer data were sent to the TR computer. As the subject used the paretic arm to rotate the pitcher, a figure of a pitcher on the video screen moved synchronously, allowing the subject to use a real object to play a game where the goal was to fill empty cups to the correct level.

(4) Daily study pill consumption: Each day, patients were also asked to consume a study pill. This pill was an unblinded placebo (small sugar-free mint). The computer screen guided patients through a series of steps to open the pill container, put the lid on the TR table, put a pill in their hand, ingest the pill, and then replace the lid; the TR camera took a picture when the patient hit a button to indicate that each step was completed, and these pictures were later used to confirmed compliance with pill intake. Pills were kept in a yellow container, clipped to the TR table, and had a lid (DoseSmart; RxCap; Boston, MA) that sent a Bluetooth signal to the computer each time the container was opened.

(5) Expanded assessments, as below.

(6) E-mail actionable reports for critical findings: The study coordinator and lead investigator were automatically sent an email (with a suggested response) if either of two conditions arose: (1) sharp increase in pain, defined as increase in the shoulder pain score by $\geq$20/100, with the suggested response being to contact the patient same day; (2) non-compliance with therapy, defined as the patient failing to initiate TR for 3 days in a row, with the suggested response being to contact the patient same day.

(7) Reliance on home WiFi: In addition, we sought to evaluate the performance of each patient's home WiFi network. In each case, the home-based TR system was connected to the internet using the patient's personal wireless network rather than a study-provided wireless cellular modem.

Study Assessments

To fully characterize enrollees, a broad range of assessments was evaluated, including measures of impairment, activities limitation, quality of life, and patient-reported measures. In addition to assessments at the four in-clinic visits, patients underwent assessments at home via the TR system, some of which were supervised by therapists and some scored with no therapist present.

The primary endpoint was the UE-FM scale (56, 57), which ranges from 0 to 66, with higher scores indicating less UE impairment. The main secondary endpoint for UE was the Box & Blocks (B&B) score (58), which counts the number of blocks a subject can lift and move across the table in 60 s. The two main LE secondary endpoints 10 meter walk test of gait velocity (59) (measured as the mean of two trials) and the LE-FM motor scale (56, 57), which ranges from 0 to 34, which higher scores indicating less LE impairment. Demographic data, medical history, and handedness (60) were obtained on study entry. The presence of aphasia was assessed using Philadelphia Naming Test (Form A) (61). The presence of neglect was assessed using the Line Cancellation Test (62).

A social network survey (PERSNET) was assessed during the live visit 6 weeks after enrollment. The results of these social network studies are presented in a separate companion paper (63).

Several additional dimensions of stroke outcome were measured at baseline and after 12 weeks of therapy: Optimization in Primary and Secondary Control (OPS) scale (64), which measures dedication to treatment goals across 12 questions, with scores ranging from 1 to 7 and higher scores reflecting greater motivation; Nottingham sensory scale (65), which assesses a range of sensory modalities in the distal UE, with maximum score of 11 and higher scores reflecting better sensory function; Geriatric Depression Scale (GDS) (66), which measures depression across 15 questions, with a maximum score of 15 and higher scores reflecting greater depression; Montreal Cognitive Assessment (MoCA) (67), which measures cognitive function, with maximum score of 30 and higher scores reflecting less cognitive impairment; modified Rankin Scale (mRS) (68), which measures global function (disability and dependence), with a maximum score of 6 and higher scores reflecting poorer function; EuroQol visual analog scale (EQ-VAS) (69), in which a subject rates his/her own health from 0 to 100 and higher scores reflect better quality of life; and modified Ashworth Spasticity (mAS) scale (70), which measures spasticity at the elbow flexor, with a maximum score of 4 and higher scores reflecting greater spasticity.

Some assessments were made by the study therapist using the TR system. Patient-reported outcomes, which are well aligned with scoring via videoconference, were examined. Hand function was measured using the Stroke Impact Scale (71) (SIS)-hand subsection, with a maximum score of 5 and higher scores reflecting better hand usage. This patient-reported outcome was measured during videoconferences in weeks 1 and in 12. Functional status was measured using the SIS-activity of daily living (ADL) subsection (71) during videoconferences in weeks 2 and in 12; the maximum score is 5, and higher scores reflect less difficulty with ADLs.

Other assessments were made by the patient, with no therapist present, using the TR system. To maximize the likelihood that the unsupervised patient at home would be successfully assessed, the focus here was on Likert scales and visual analog scales. The MOS Social Support Survey (72) (MOS-SSS) was scored via the TR system during week 2; scores range from 19 to 95, with higher scores reflecting stronger social support. The Brief Resilience Scale (73) was also scored via the TR system during week 4; maximum score is 30, with higher scores indicating better resilience. The Generalized Anxiety Disorder-7 (74) (GAD-7) scale was also scored via the TR system in week 3; maximum score is 21, with higher scores reflecting greater anxiety. Finally, shoulder pain and fatigue were assessed weekly with a focus on the first 6 weeks, using a visual analog scale (0–100) where higher numbers indicate greater pain and fatigue, respectively.

Some assessments were scored by the therapist at both a live visit and during a TR videoconference, in order to validate telehealth screening. Measures of mood and language were selected given the expectation that patients would likely be stable in these domains across the 1–3 weeks when serial testing was performed. The GDS score was scored during a week 9 videoconference and a week 12 in-clinic visit. The Philadelphia Naming Test (61) short form was scored twice; the maximum score is 30, and higher scores reflect less aphasia. Form A was scored during the live week 6 visit; Form B, which assesses 30 different objects, was scored by the therapist 1 week later, during a videoconference.

Data Analysis

Data analysis used non-parametric statistical testing (JMP 13, SAS; Cary, NC). Statistical moments are presented as median (IQR). All analyses were two-tailed, with statistical significance set at $p < 0.05$ and no corrections made for multiple comparisons in this feasibility study. Within-subject changes in performance over time were analyzed using the Wilcoxon Signed Rank Test. Comparisons of subject values in weeks 1–6 vs. weeks 7–12 were analyzed using the Wilcoxon Rank Sums Test. Comparisons of two continuous variable were performed using the Spearman Rank Correlation Coefficient. For some telerehab-based assessments, data were missing for 1 subject; missing data were not imputed.

RESULTS

Subjects

A total of 15 subjects were screened, of whom 13 were enrolled. Each was assigned 72 treatment sessions and 18 videoconferences with a study therapist, distributed over 12 weeks. For all subjects, the home WiFi network consistently supported TR data uploads and downloads as well as videoconferences. Of the 13 patients, nine received concomitant therapy outside of study procedures at some point during the study: seven at baseline; seven at 6-weeks, and eight at 12 weeks. There were no adverse events.

Subjects were a median of 61 years old and 4 months post-stroke at study entry (**Table 2**); 5 patients were <90 days post-stroke (range, 37–67 days), 8 patients were ≥90 days (range, 119–1,682), and 4 patients were >1 year post-stroke (range 16–56 months). Nine subjects were White, 3 Asian, and 1 African-American. One subject was Hispanic. All subjects had completed high school, with a median of 2 additional years of education. No patient had aphasia or spatial neglect.

Therapy Dose and Compliance

Patients completed 50.4 h (33.3–56.7) of TR over the 12 weeks, and attended a median of 16 (14–18) videoconferences. Patients initiated the daily TR session (did >5% of assigned minutes) on 79.9% of days, and completed most of the session (did >50% of assigned minutes) on 65.7% of days. Common reasons for missed therapy sessions were vacation (55), demands from the patient's job (40), scheduling conflicts (32), and illness (22).

Compliance declined across the 12 weeks of therapy. Comparing weeks 1–6 with weeks 7–12: session initiation decreased from 86.4 to 73.5% ($p < 0.0001$; **Figure 1A**); and session completion decreased from 76.9 to 54.6% ($p < 0.0001$; **Figure 1B**), i.e., non-compliance doubled in the second 6-week block. The rate of session completion across the 12 weeks did not vary in relation to time post-stroke ($r = 0.28$, $p = 0.36$), age ($r = 0.33$, $p = 0.27$), or baseline scores on the GDS ($r = -0.38$, $p = 0.2$), MoCA ($r = -0.28$, $p = 0.35$), or UE-FM ($r = -0.41$, $p = 0.17$). Although the content and quantity of assigned therapy was constant over time, subjects completed a median of 61.5 (IQR =

33–65.8) min/day of therapy during weeks 1–6 vs. 43.6 (2–63.3) min/day during weeks 7–12 ($p < 0.0001$). Subjects engaged in free play after finishing their assigned therapy on 1/5 days during weeks 1–6 but only 1/16 days during weeks 7–12 ($p < 0.0001$).

In-clinic Assessments

TR was associated with significant UE motor gains. From baseline pre-therapy to follow-up after 12 weeks of TR therapy, the primary endpoint, UE-FM score, changed by 6 (2.5–12.5) points ($p = 0.0005$). Most of this change was achieved in the first 6 weeks, as UE-FM score change from baseline to week 6 was 6 (2–9.5) points ($p = 0.0007$). From week 6 to week 12, median change was 1 (−0.5 to 2) point ($p = 0.19$). The extent of 12-week gains on the UE-FM scale declined with increasing time post-stroke at enrollment ($r = -0.63$, $p = 0.02$). Similar gains were seen from baseline to week 12 for change in affected arm Box & Blocks score, with median change of 9 blocks (3.5–17.5) ($p = 0.0005$). Median change in unaffected arm Box & Blocks score during this interval was non-significant [2 blocks (−5 to 4.5) ($p = 0.69$)].

Findings were similar for the LE. Gait velocity improved by a median of 0.15 (0.07–0.22) m/s from baseline to week 12 ($p = 0.0007$). Most of this change was achieved in the first 6 weeks, where change from baseline was 0.08 (0.02–0.20) m/s ($p = 0.007$). Results were more modest for the LE-FM score change, which was 1 (−0.5 to 5) point ($p = 0.065$) over 12 weeks.

Several other classes of outcome measure also showed improvement. Scores on the mRS ranged from 2 to 3 at baseline and from 1 to 2 at week 12 (change over time, $p = 0.03$). This change was accounted for by improved mRS score in 6/13 patients (five with initial score = 3 and one with initial score = 2), 3 of whom were <90 days post-stroke (37–67 days) and 3 of whom were >90 days post-stroke (4, 5.5, and 56 months post-stroke) at study enrollment. In addition, the EQ-VAS increased from baseline to week 12 by a median of 15 (2.5–31), indicating improved self-rating of health state. Mood (GDS) improved over time ($p = 0.05$); note that a GDS score > 5, suggesting depression, was present in 3 subjects at week 1 and 0 subjects at week 12.

TABLE 2 | Patient values at baseline.

	Baseline
N	13
Sex	9 M/4 F
Age	61 [52–65.5]
Time post-stroke (days)	129 [52–486]
BMI	26.6 [24.8–32.3]
Systolic blood pressure (mm Hg)	120 [118–134]
Diastolic blood pressure (mm Hg)	75 [72–80]
Hypertension	10 Yes
Hypercholesterolemia	7 Yes
Diabetes mellitus	4 Yes
Atrial fibrillation	2 Yes
Affected side	10 L/3 R
Shoulder pain present at baseline	8 Yes
Handedness	10 R/3 L
Optimization in Primary and Secondary Control scale	5.6 [5.1–6.0]
MOS Social Support Survey*	83 [69–92]
Brief Resilience Scale*	23.5 [22.25–26]
Generalized Anxiety Disorder-7*	3 [0–8.5]

Values are median (IQR).
**Data acquired via the TR system, with no therapist present.*

Remote Assessments

There were three types of remote assessments (**Table 3**). First, therapist-directed measures during videoconferences captured behavioral gains. Hand usage, measured using the SIS-hand scale,

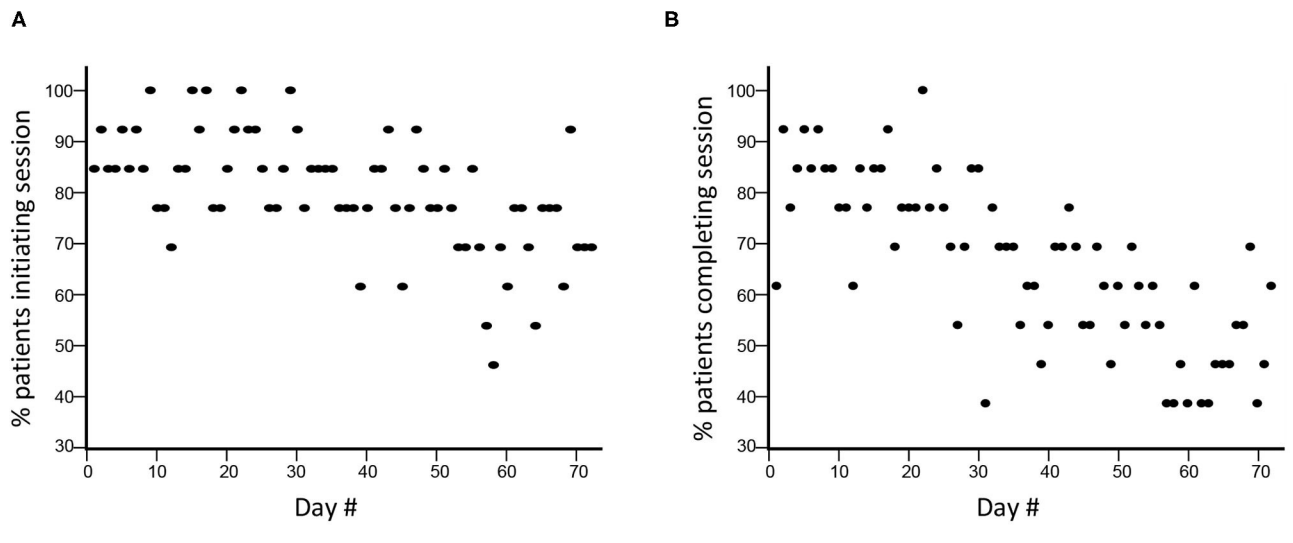

FIGURE 1 | Compliance with TR assignments declined during the 12 weeks. **(A)** During TR weeks 1–6 (days 1–36), there was a decline in TR session initiation compared to weeks 7–12 (days 37–72), from 86.4 to 73.5% ($p < 0.0001$). **(B)** There was a similar decline in in TR session completion, from 76.9 to 54.6% ($p < 0.0001$).

TABLE 3 | Behavioral change after 6 and 12 weeks of treatment.

	Baseline	After 6 weeks of treatment	$p^{\wedge}$	After 12 weeks of treatment	$p^{\wedge\wedge}$
Arm motor Fugl-Meyer score	46 [42–57]	57 [50–61]	0.0007	59 [52.5–61.5]	0.0005
Box & Blocks score, affected arm	32 [23–42.5]			46 [39–50]	0.0005
Box & Blocks score, unaffected arm	55 [48.5–57]			53 [47.5–61.5]	0.69
Gait velocity [m/sec]	0.94 [0.67–1.09]	0.90 [0.71–1.2]	0.007	1.01 [0.83–1.21]	0.0007
Leg motor Fugl-Meyer score	28 [23.5–29]	27 [26–29.5]	0.48	28 [27–30.5]	0.065
Nottingham sensory score, affected arm	11 [10–11]			11 [11–11]	0.12
Geriatric Depression Scale score	3 [1–5]			1 [0–4]	0.05
Montreal Cognitive Assessment score	27 [24.5–29]			29 [25.5–30]	0.13
Modified Rankin Scale	2 [2–3]			2 [2–2]	0.03
EQ-VAS	75 [52.5–80]			80 [72.5–90]	0.003
Modified Ashworth spasticity scale, elbow flexor	1.5 [0.5–1.5]			1 [0–1.25]	0.11
Stroke Impact Scale-hand*	3.4 [2.7–3.9]			4.0 [3.5–4.8]	0.002
Stroke Impact Scale-ADL*	3.8 [3.1–4.4]			4.2 [4.0–4.5]	0.06

Values are median (IQR); p values are based on Wilcoxon Signed Rank Test for change over time from baseline to ^6 weeks or baseline to ^^12 weeks.
**Data acquired via the TR system, with therapist supervision.*

showed significant gains ($p = 0.002$). Functional status, measured using the SIS-ADL scale, showed improvement over time that narrowly missed significance ($p = 0.06$). Second, therapist-independent measures (no therapist online when scored) reliably assessed patient status. Median score on the MOS-SSS was 83 (69–92), indicating strong social support on average. Median score on the Brief Resilience Scale was 23.5 (22.25–26), indicating overall good resilience. Median score on the GAD-7 scale was 3 (0–8.5), indicating low anxiety on average. Scores for shoulder pain were stable from week 1 to week 6, rising slightly, from 0 (0–31) to 9 (0–25) ($p = 0.46$) on this 100-point visual analog scale. Fatigue, however, declined significantly from week 1 to week 6, from 36 (8–61) to 16 (0–43) ($p = 0.004$). Third, for two assessments, therapist scores obtained in-clinic were compared to those obtained during TR. The two sets of GDS scores obtained 3 weeks apart were closely related ($r = 0.89$, $p < 0.0001$; **Figure 5**) and showed an intraclass correlation coefficient of 0.66; note that one subject was not available for the week-9 videoconference. Findings on the Philadelphia Naming Test had a ceiling effect that limited comparisons, as scores on Form A in-clinic were perfect in all but two patients and scores on Form B via TR were perfect in all but three patients.

Augmented Reality Gaming and Application of Sensors to Real Objects

Augmented reality was successfully incorporated into home-based TR. The equipment was installed in the home, the AR game assigned by the therapist, and these were used by patients during TR (**Figure 2**). Similarly, an accelerometer could be applied to various objects by the patient at home (**Figure 3**), allowing movement of a real object in a functional way to play a game that emphasized iADLs.

Daily Study Pill

Consumption of a study pill once/day (**Figure 4**) was successfully incorporated into TR sessions. One subject requested not to have any photos taken. The remaining 12 subjects used their TR system on 681 days, and took their pill on 619 of these days, resulting in 90.9% compliance with daily study pill consumption. The Bluetooth-enabled pill bottle cap worked properly but there were difficulties keeping its software running at all times in the background of the TR program.

Automatic Actionable Reports by Email for Critical Findings

Email-alerts were sent to the PI and to the study coordinator reliably and with specificity whenever there was (1) a substantial increase in body or shoulder pain or (2) non-compliance with therapy for 3 days. During the study, reportable incidents only occurred in relation to non-compliance.

DISCUSSION

High dose rehabilitation therapy can improve outcomes after stroke, but this is not provided to many patients. Telehealth methods have the potential to overcome many of the barriers to high dose therapy, such as transportation limitations or limited regional access. In an effort to improve our approach to home-based TR, the current study aimed to evaluate the feasibility of several system expansions related to assessment and to treatment.

Enrollees were recruited at wide-ranging times post-stroke, had overall moderate motor deficits and little sensory deficits, were highly dedicated to treatment goals, lacked cognitive deficits, had low anxiety and depression symptoms, had good social support, and reported high resiliency (**Tables 2**, **3**). In our prior studies, we relied on a Verizon wireless modem to connect the patient's home-based TR system to the internet and thereby enable communication between the home and the clinic. The current study found that we can instead rely on the patient's personal wireless network, an approach that, when available, has advantages such as connection speed.

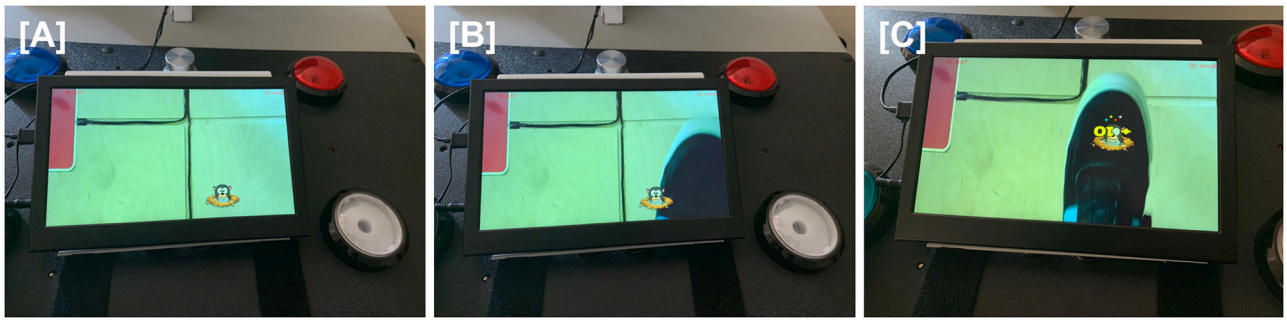

FIGURE 2 | For the virtual varmint game, a camera under the table pointed at the floor captured live images, including the patient's paretic foot, that were projected onto the screen of a tabletop tablet. When patients directed their gaze at the tabletop, they were thus able to see real-time images of their foot movements. A virtual varmint was introduced into the tablet image, which the patient was able to manipulate with their foot. **(A)** A virtual image of a varmint is introduced onto the screen of the tabletop tablet. **(B)** The patient moves his foot toward the virtual varmint. **(C)** The patient swats the virtual varmint with his foot, scoring points.

Across the 12 weeks of TR, UE and LE motor status, functional status, and quality of life all improved significantly (**Table 3**), particularly during the first 6 weeks. These gains occurred as patients completed a median of 50.4 h/subject of TR. Some of this improvement might be related to spontaneous post-stroke recovery. Five of the 13 enrollees were <90 days post-stroke at enrollment, and so some of their behavioral improvement is likely attributable to spontaneous recovery; consistent with this, UE-FM gains declined with greater time post-stroke.

Longer Therapy Duration

Our prior trial (48) evaluated 6 weeks of therapy provided 6 days/week (70-min sessions, 42 h total). Here we aimed to evaluate a course of TR lasting for twice as long: 12 weeks of therapy (60-min sessions, 72 h total). This was driven in part by our review of home-based technologies for stroke rehabilitation (75), which noted that across 31 studies, most technologies were evaluated for short time periods. In addition, larger doses of TR have been reported to result in greater benefit (76).

The rate with which subjects initiated (**Figure 1A**) and completed (**Figure 1B**) TR assignments declined significantly across the 12 weeks of therapy. During TR weeks 1–6, TR session completion was 76.9%, lower than the 98.3% value seen during a 6-week course of telerehabilitation in our 11-site study (48). Compliance was not related to time post-stroke, age, depression, cognitive status, or arm motor impairments at baseline, although the sample size is limited for examining these issues. Several reasons might account for lower compliance over time seen in the current study. Functional gains during the first 6 weeks might have reduced motivation to perform TR thereafter. Patients might have become bored with some games. During weeks 7–12, videoconferences were reduced from 3x/week to 1x/week, due to budgetary constraints, which might have contributed to the doubling of non-compliance during this period. These videoconferences were a stimulus for patient accountability, and so a reduction in their frequency might have adversely affected compliance. In addition to driving accountability, videoconferences also foster a relationship between patient and therapist that might be important to sustained compliance. In a qualitative study (77) of 13 patients randomized to TR at one site in our national trial, regular videoconferences with a therapist were highly rated. Fewer interactions during videoconferences might produce weaker patient-therapist bonds, contributing to non-compliance.

Treatment of Both UE and LE Motor Deficits

This study also examined the feasibility of treating both UE and LE motor deficits. While not all stroke survivors have motor deficits in both UE and LE, involvement of both is more common than is paresis in either alone (78). Despite this, only 2 of the 22 stroke TR trials have targeted both UE and LE deficits (45). The current study found that exercises and games targeting LE motor deficits were readily incorporated alongside those targeting UE, and were associated with significant gains in gait velocity.

Increasing the Functional Relevance of TR

Practice of real life tasks with real objects can increase object affordance and task ecology and is often incorporated into constraint induced therapy (51). The TR system is well suited to adopt this strategy. The current study found that a sensor could be attached to real objects, providing data that are used to drive game play that targeted pouring liquids (**Figure 3**), which is part of meal preparation, an important iADL.

An additional way to expand the functional relevance of TR therapy is to incorporate virtual objects that may be impractical or unsafe in the patient's home. AR integrates virtual elements into the real world (54) and was successfully incorporated into the TR system (**Figure 2**). AR introduces an additional form of human-computer interface that can be used to modulate a task's cognitive demand (55).

Daily Consumption of a Study Medication Integrated Into TR

Daily ingestion of a study pill was integrated into the home-based TR system. Patients were prompted to take a study pill at the start of each session and did so 90.9% of the days that they initiated a TR session (**Figure 4**). Driving patient compliance

FIGURE 3 | Sensors were attached to real objects to play a game that drives an iADL. The patient grasped an actual water pitcher onto which an accelerometer (green arrow) was attached magnetically. Accelerometer data were sent to the computer running the TR program. As the subject rotated the hand-held pitcher, the figure of a pitcher on the video screen moved synchronously. In this way, the subject used a real object to play a game, displayed on the TR computer screen, where the goal was to fill empty cups to the correct level.

FIGURE 4 | Photographs were used to confirm that the study pill was taken each day as instructed. **(A)** The patient is seated; arrow indicates cap on the bottle holding study pills. **(B)** The patient has removed the pill bottle lid and placed onto the trackpad; arrow indicates the lid. **(C)** The patient has removed one pill and placed into her palm; arrow indicates the pill. **(D)** The patient has taken the pill. **(E)** The lid has been replaced; arrow indicates the lid.

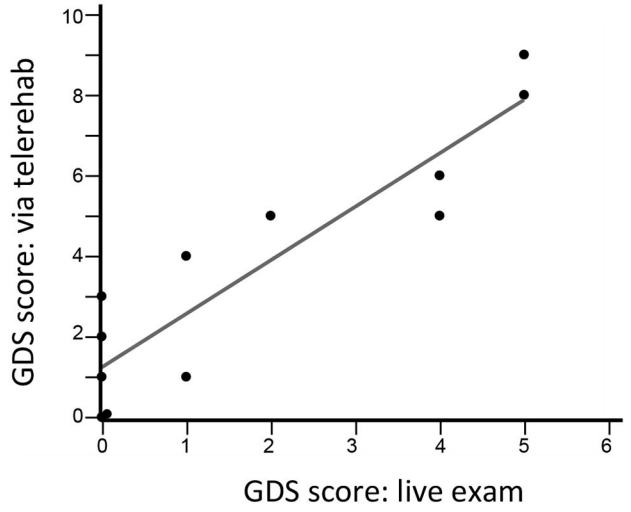

FIGURE 5 | GDS scores during a live visit 12 weeks after study entry are closely related to GDS scores obtained during a TR videoconference 9 weeks after study entry ($r = 0.89$, $p < 0.0001$, $n = 12$). The intraclass correlation coefficient was 0.66.

with pill consumption each day might be useful in clinical practice, e.g., to improve secondary stroke prevention or in clinical research, e.g., when studying an orally ingested drug that might promote recovery, particularly since TR enables careful pairing of behavioral training with pill consumption (79–81).

Additional TR-Based Assessments

TR not only provides an opportunity for remote therapy but also provides a platform for remotely measuring, both passively and actively (82), a broad range of human activities (83) and behavioral and psychological symptoms (84). This can promote greater independence and quicker access to healthcare professionals (85). The current results support the feasibility of using TR to measure hand usage (SIS-hand) and functional status (SIS-ADL). The GDS was validated for depression telescreening (**Figure 5**); interestingly, average scores at home were higher compared to when the same scale was administered in the clinic, in contradistinction to prior results obtained in a non-stroke population (86).

We evaluated four assessments that were scored asynchronously, i.e., by the patient with no therapist supervision, and all were successfully collected. These include the MOS-SSS, which indicated strong social support; the Brief Resilience Scale, which showed overall good resilience; and the GAD-7, which showed low anxiety scores. In addition, shoulder pain and fatigue were assessed weekly. Shoulder pain, the most common adverse event in patients randomized to TR in our prior national trial (48), was mild and stable over 6 weeks. Patients reported a significant decline in fatigue over time.

TR-Generated Actionable Reports

A very large amount of data is generated by the TR system. Efficient approaches are needed to bring the most critically important findings to the attention of busy clinicians. We incorporated actionable reports, whereby a clinician is notified electronically of a critical finding, along with a suggested response. Electronic notification of critical results has advantages that include decreased workflow interruptions and more timely closed-loop communications of key patient data (87). Such reports are most effective when recommendations presented to clinicians are clear, explicit, and actionable (88). Such reports should focus on high quality observations that present critical new knowledge (89). Communication of critical results is a national patient safety goal emphasized by the Joint Commission, and is no less important in stroke recovery. The current pilot study provides support for actionable results to transmit critical findings in two categories, pain and treatment compliance.

Strengths and Weaknesses

Strengths of this feasibility study include successful evaluation of several new expanded TR features related to treatment and to assessment, including longer-term therapy, addition of therapy targeting the LE, increased dimensions of assessments, incorporation of real objects and AR, and introduction of a daily study pill. There were several key weaknesses, as well. The sample size was limited. As this was a feasibility study, there was a single treatment arm and no control group. Some patients might not have completed spontaneous recovery at study entry, although the goal was to evaluate new TR features rather than establish efficacy. The total number of daily limb movements during TR was not measured, as in our prior studies. No qualitative study was performed to better understand the perspectives of patients and caregivers. Current results incompletely generalize, as enrollees lacked substantial aphasia, neglect, sensory deficits, depression, and anxiety.

Conclusions

The current study examined the feasibility of adding new modules to a home-based TR system for patients with stroke. Some modules were therapy-focused, such as longer duration of therapy and ingestion of daily study medication, while others were diagnostic, such as assessments performed by the patient with no therapist supervision. These results inform future efforts to develop TR approaches to address the many aspects of treating patients with stroke.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by UC Irvine IRB. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

The study was designed by SC, LD, AM, JS, RA, RZ, AD, WS, and JH. The study was conducted, the manuscript was written, and critically revised by all authors.

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A Virtual, Randomized, Control Trial of a Digital Therapeutic for Speech, Language, and Cognitive Intervention in Post-stroke Persons With Aphasia

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Background: Post-stroke aphasia is a chronic condition that impacts people's daily functioning and communication for many years after a stroke. Even though these individuals require sustained rehabilitation, they face extra burdens to access care due to shortages in qualified clinicians, insurance limitations and geographic access. There is a need to research alternative means to access intervention remotely, such as in the case of this study using a digital therapeutic.

Objective: To assess the feasibility and clinical efficacy of a virtual speech, language, and cognitive digital therapeutic for individuals with post-stroke aphasia relative to standard of care.

Methods: Thirty two participants completed the study (experimental: average age 59.8 years, 7 female, 10 male, average education: 15.8 years, time post-stroke: 53 months, 15 right handed, 2 left handed; control: average age 64.2 years, 7 female, 8 male, average education: 15.3 years, time post-stroke: 36.1 months, 14 right handed, 1 left handed). Patients in the experimental group received 10 weeks of treatment using a digital therapeutic, Constant Therapy-Research (CT-R), for speech, language, and cognitive therapy, which provides evidence-based, targeted therapy with immediate feedback for users that adjusts therapy difficulty based on their performance. Patients in the control group completed standard of care (SOC) speech-language pathology workbook pages.

Results: This study provides Class II evidence that with the starting baseline WAB-AQ score, adjusted by −0.69 for every year of age, and by 0.122 for every month since stroke, participants in the CT-R group had WAB-AQ scores 6.43 higher than the workbook group at the end of treatment. Additionally, secondary outcome measures included the WAB-Language Quotient, WAB-Cognitive Quotient, Brief Test of Adult Cognition by Telephone (BTACT), and Stroke and Aphasia Quality

of Life Scale 39 (SAQOL-39), with significant changes in BTACT verbal fluency subtest and the SAQOL-39 communication and energy scores for both groups.

Conclusions: Overall, this study demonstrates the feasibility of a fully virtual trial for patients with post-stroke aphasia, especially given the ongoing COVID19 pandemic, as well as a safe, tolerable, and efficacious digital therapeutic for language/cognitive rehabilitation.

Clinical Trial Registration: www.ClinicalTrials.gov, identifier NCT04488029.

Keywords: tele-neurorehabilitation, post-stroke aphasia, virtual treatment, language outcomes, remote assessment

INTRODUCTION

According to the Centers for Disease Control and Prevention (CDC), every year an estimated 795,000 Americans will have a stroke, and more than 180,000 will be left with communication disorders such as aphasia (1, 2). Aphasia can impact a person's ability to understand and follow instructions or read a prescription label. It can isolate a person from their family and friends, impacting their sense of self and bringing with it a myriad of other loneliness-related health risks (3).

Aphasia is a chronic condition that requires ongoing rehabilitation (4). It was once thought that recovery only occurred in the first year of a stroke; however, a growing body of evidence shows that people with aphasia (PWA) can continue to improve with ongoing rehabilitation even many years after their injury (4, 5). A recent Cochrane review suggests that functional communication significantly improves when one receives speech-language therapy at a high intensity, across several sessions, or over a long period of time (6). Despite the evidence that supports the need for ongoing therapy, there are not enough therapists who can treat post-stroke aphasia. The expectation for therapists to provide therapy five times per week during the chronic phase of care is simply not feasible. In addition to limited access to therapists, other barriers that patients experience include limited insurance coverage, lack of transportation, distant geography, schedule constraints, and fatigue (7). As a result, rehabilitation for aphasia patients is quite fragmented (8), or insufficient, especially for stroke survivors living in the community but not in active therapy (4) which ultimately leads to worse patient outcomes, especially when they can benefit from ongoing therapy post-discharge. Since the COVID19 pandemic began, individuals with aphasia have faced even greater hurdles in accessing the care they need due to safety restrictions exacerbating disparities in healthcare for these individuals (9).

Teletherapy, or technology assisted/delivered therapy, provides an alternative to the brick-and-mortar approach of delivering rehabilitation services (10–14). In such an approach, therapy is delivered via a computer and over the internet asynchronously but follows the same basic principles of traditional person-to-person rehabilitation. A clinician can also supervise teletherapy sessions remotely. Early indications illustrate that such technology would afford PWA greater opportunity for consistent and intensive practice, especially when coming into the clinic is not feasible (15, 16). Further, teletherapy may also allow long-term continued rehabilitation to be more accessible for PWA. While some aphasia research highlights the limitations in using technology with this population (17, 18), other research demonstrates positive outcomes in improving language skills with technology (19–22). Recent systematic reviews have examined different technology-based rehabilitation delivery options for both cognitive deficits (23, 24) and language deficits (25–28). Further, a recent RCT specifically compared treatment outcomes for PWA receiving self-managed computerized speech therapy relative to other control treatments (20). In this study, 278 PWA were assigned to either daily self-managed computerized speech language therapy plus usual care (experimental, CSLT group), usual care (usual care group), or attention control plus usual care (attention control group). Treatment was completed for 6 months and results showed that the experimental group receiving computerized therapy (CSLT) demonstrated significantly higher gains in trained word finding relative to the two control groups, however, there was no evidence of generalization to untrained words. Further, there were no differences in functional communication or participants' perception of their own communication or participation across the three intervention groups. Nonetheless, these results add to the emerging premise that remote or home-based computerized therapy can be a valid approach to deliver rehabilitation to individuals with post-stroke aphasia.

In our prior work with teletherapy, we have examined the feasibility and clinical efficacy of Constant Therapy-Research (CT-R[1]), a digital therapeutic software program accessible through a tablet (29–31). CT-R is a prototype based on the commercially available Constant Therapy product. In a previous study, 51 subjects (42 experimental, 9 control) utilized the Constant Therapy software platform under the systematic monitoring and guidance from their clinician during weekly in-clinic sessions (29). The experimental group had access to Constant Therapy both at home and during in-clinic sessions,

[1]CT-R was referred to as "PCT" within IRB documentation and ClinicalTrials.gov registration. It was internally renamed as CT-R for clarity and is otherwise identical to PCT.

while the control group only utilized the application during in-clinic sessions. After 10 weeks of intervention, experimental participants were significantly more engaged in their therapy and practiced an additional 4 h per week on average compared to the in-clinic therapy sessions, where participants received an average of 40 min per week. In addition, experimental participants showed significantly more improvements on Constant Therapy tasks and on standardized language and cognitive tests than control participants. Separately, in a retrospective analysis of Constant Therapy home users vs. clinic users (31), both home and clinic users required roughly the same amount of practice to successfully complete cognitive and language tasks, but users who had on-demand access to therapy on their tablet mastered tasks in a median of 6 days, while those with only in-clinic access mastered tasks in a median of 12 days. Further, users who had access to digital therapy at home practiced at least every 2 days, while clinic users practiced in the clinic just once every 5 days. These findings suggest that Constant Therapy users were able to practice structured therapy at home, which provided them with greater practice and greater intensity of therapy than patients receiving the same therapy in clinic. These studies also highlighted the potential for a home-based therapy program for patients who are unable to receive consistent in-clinic therapy.

The primary objective of this study was to examine the efficacy of CT-R practiced under the remote-guidance of a study personnel when compared to an active control group that practiced aphasia therapy workbooks. Our rationale was that self-management of home-based therapy under remote-guidance that included an individualized therapy protocol would lead to increased adherence and compliance of home practice, and ultimately improved language and cognitive skills. We conducted a Phase II, randomized decentralized (virtual) trial, in which 36 participants (stroke survivors with aphasia) received either language therapy at home delivered through CT-R or practiced aphasia therapy workbooks at home. Both groups received baseline and follow-up assessments, as well as periodic therapy check-in sessions, through video conference sessions. The primary outcome of the study was change in the Western Aphasia Battery-R Aphasia Quotient (WAB-R AQ) (32). The primary hypothesis was that self-managed, digital therapy under remote supervision would result in systematic and structured reinforcement-based practice of impairment based therapy, which would ultimately lead to greater language outcomes, as compared to the control group that did not receive this systematic structured practice. Additionally, to the best of our knowledge, this is the first fully virtual language therapy study for individuals with aphasia.

METHODS

Recruitment

As this was a completely virtual study, participants were recruited from the United States and Canada from March 2019 to November 2019. The following were sources of participant recruitment: (a) consumers who had downloaded the commercially available Constant Therapy app but not signed up for an account, (b) social media groups focused on recovery from aphasia, and (c) referrals from SLPs who had discharged clients from their service. Recruitment was conducted via email, video advertising, flyers, and social media posts.

Participants

Inclusion criteria included (a) diagnosis of stroke involving a hemorrhage or ischemic event, resulting in speech, language, and/or cognitive deficits as confirmed by medical records; (b) time post-stroke of at least 4 months prior to enrollment; (c) having been discharged from the hospital or rehabilitation center; (d) being aged 18 years or older at the time of consent; (e) being a fluent English speaker prior to stroke; (f) having confirmed aphasia based on the Western Aphasia Battery, Revised (WAB-R) (32) Aphasia Quotient with a score of 90 or lower (normal cutoff score is 93.8), and (g) the presence of a family member or caregiver willing and able to provide assistance during the duration of the study period.

Exclusionary criteria included (a) comorbid neurological conditions that could impair study performance in the opinion of research staff (either a certified Speech-Language Pathologist or a trained Research Assistant), (b) requiring inpatient care or acute care at the time of the study, (c) concurrently undergoing one-on-one individual therapy at a hospital or rehabilitation facility, university, or at home, (d) presence of severe apraxia of speech or severe dysarthria of speech based on clinical screening, (e) comorbid psychiatric conditions that could impair study participation in the opinion of study staff, and (f) uncorrected vision or hearing loss impairing study participation.

A pre-screening phone call was conducted by the research staff with the participant and caregiver to discuss the details of the study and participant characteristics. Then, each participant was mailed materials that included: an iPad tablet, WAB-R assessment items, informed consent and medical release forms, and a pre-addressed and stamped envelope to return consent and release forms. Following informed consent, participants were evaluated utilizing Part 1 of the WAB-R following procedures for videoconference assessment (33). If all eligibility criteria were met, the participant was enrolled in the study. Of the 58 participants that were screened against eligibility criteria, 36 were enrolled and 32 completed the study (see **Figure 1**). Of those who completed the study, the mean age of participants was 61 years ($SD = 10$), 18 participants were male, the average time post-stroke was 46 months ($SD = 47$), and the mean years in education was 15 years ($SD = 2.6$). As noted above, all participants completed all parts of the study from their homes.

Primary and Secondary Outcome Measures

The primary outcome measure utilized was the Western Aphasia Battery, Revised (WAB-R) Aphasia Quotient (WAB-AQ) (32). The WAB-R is a standardized tool that assesses language and cognitive skills and provides scores quantifying the impact of a stroke on those skills. The WAB-AQ from the WAB-R includes segments from Part 1 of the assessment, evaluating fluency and information content within spontaneous speech, auditory comprehension, naming, and repetition. The Language and Cortical Quotients obtained from the WAB-R (WAB-LQ and

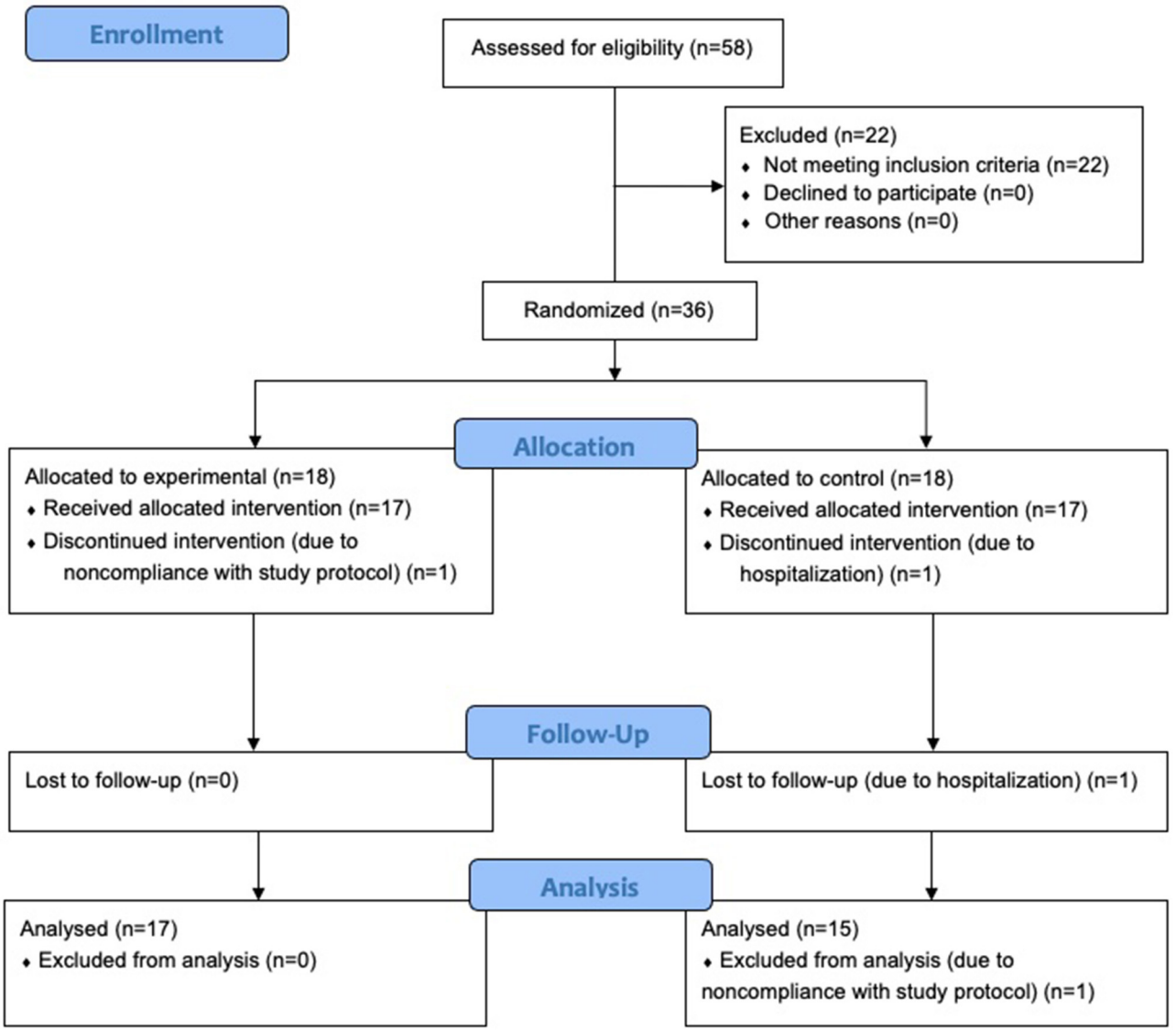


FIGURE 1 | Consort participant flow diagram.

WAB-CQ) Parts 1 and 2 were utilized as secondary outcome measures. Part 2 of the WAB-R includes reading, writing, apraxia, constructional, visuospatial, and calculation sections.

Additionally, secondary measures included scores on the Brief Test of Adult Cognition by Telephone (BTACT) (34, 35), a brief, remote, cognitive assessment that evaluates memory for and judgments about words and numbers (including recall tasks, both immediate and short term, category fluency, and number reasoning and manipulation tasks), and the Stroke and Aphasia Quality of Life Scale 39 (SAQOL-39) (36, 37). The SAQOL-39 is a structured quality of life questionnaire administered to either a patient or a caregiver to assess the impact of a stroke on daily activities, communication, emotions, and family and social life by asking patients or caregivers to complete a 5-point rating scale in response to specific questions focusing on the past week alone. All the above measures were chosen based on prior evidence for having been administered remotely, either by videoconference or by phone (33, 35, 38, 39).

Assessments

Following informed consent, and the administration of the WAB-R, if the participant met eligibility criteria of an aphasia quotient of 90 or below, the remainder of the assessments were completed. For participants who were identified with potential dysarthria or apraxia, the Screen for Dysarthria and Apraxia of Speech was then completed to exclude any participant that received a "severe" score on the three features of diadochokinesis, word length, and oral apraxia. Subsequently, assessment continued on with the second portion of the WAB-R,

the BTACT (34) and SAQOL-39 (39). When needed, the SAQOL-39 proxy form was provided to the caregiver to complete on behalf of the participant. As the clinician was remote, a caregiver was present with the participant during the virtual assessment to facilitate video conferencing setup and test administration. At the start of the assessment, a brief training was provided to the participant and caregiver on the videoconferencing technology. Instruction was provided to the caregiver to refrain from providing cues or hints to test items. At the conclusion of the assessment, a follow-up phone call was scheduled with the participant and caregiver within the same week to discuss next steps for participation in the study. See **Table 1** for demographic information on study participants, and **Table 2** for pre-treatment assessment data.

Study Design

Given the preliminary nature of the treatment protocol in this study, one of the purposes of this study was to generate effect sizes for future definitive clinical trials. Hence, this paper does not report apriori sample size estimates. The study participation lasted ∼14 weeks, which included: recruitment and baseline assessment (−2 to 0 weeks), treatment period (0–10 weeks), bi-weekly check-ins (weeks 2, 4, 6, and 8) and follow-up assessment (10–12 weeks). As noted, the entire study, including recruitment, enrollment, and study interventions was conducted remotely (i.e., at participant homes). The primary and secondary outcomes (WAB-R, BTACT, and SAQOL-39) were remotely administered at baseline (Week 0) and post-intervention (Week 10–12). After pre-assessment, stratified randomization was applied to assign participants into one of two groups (experimental or control) to balance for overall aphasia severity (WAB-AQ). Thus, the design was a parallel 1:1 allocation ratio with an initial random-numbers table to generate an allocation sequence that was then balanced for aphasia severity during assignments. Given the nature of the two interventions and the bi-weekly check-ins that relied on the nature of intervention, no attempt was made to blind participants or experimenters in the study. However, pre-treatment and post-treatment assessments were administrated by a team of study staff randomly assigned to participants from either group. Further, fidelity and reliability in testing administration was conducted and is described below. To encourage participation and retention, tablets were supplied with active cellular data plans, and training for how to use the tablet and app was provided to the participant and caregiver as needed.

Experimental Group (CT-R)

Participants were instructed to use a provisioned tablet with the app pre-installed. Constant Therapy (www.constanttherapy.com) provides systematic and structured therapy analogous to what is typically provided by a speech-language pathologist (SLP) that can be accessed by the patient from any location using a supported device. The NeuroPerformance Engine (NPE), a patented technology, enables the product to optimize therapeutic delivery (i.e., progress across tasks or reduce the level of difficulty) based on a patient's individual performance. An initial homework schedule was created and assigned by the study team according to each individual's WAB-R performance with guidelines that were standardized based on score cut-offs across participants. From that point, the individual was advanced via NPE algorithm using the library of therapy exercises within the CT-R app. Across exercises, there are over 100,000 stimuli within 350+ levels of difficulty spanning 9 different cognitive, speech and language domains (see **Figure 2**). Participants were instructed to use CT-R for at least 30 min a day and at least 5 days a week. CT-R tracked usage of the program so that research staff could access automated reporting of participant use to monitor participant adherence to the treatment program (29, 31).

Control Group (Workbooks)

Participants were provided with a regime of standard, paper workbooks (40–44) used for homework practice, a substantial modification from the workbooks used in the usual care control group in the BIG CACTUS study (20) that used crossword puzzles. The progression of homework went from Workbook for Aphasia (40) to the Speech Therapy Aphasia Rehabilitation Workbooks (41–43) or the Workbook of Activities for Language and Cognition (WALC 1) (44) based on feedback about difficulty. Control participants were instructed to complete at least 1 exercise within the workbook at least 5 days a week.

On a bi-weekly basis from Weeks 2 through 8, the experimental and control group participants completed a video conference check-in with a member of the research staff. During these check-ins, participants were asked to report how often they logged into CT-R to complete their exercises (experimental group) or how many workbook pages had been completed that week (control group). In addition, they were asked if they found any exercises or items too challenging or too simple. For the experimental group, as needed, the research staff modified the experimental group's homework program and documented changes. For the control group, if a participant reported that their workbook was too easy or too difficult, a correspondingly different workbook was sent to them. Details of the two interventions are provided in **Table 3**.

Data Reliability and Data Analysis

Data Entry

All assessments were scored utilizing hard copies of the WAB-R, BTACT, and SAQOL at the time of administration. Study personnel then checked and entered these scores into a shared spreadsheet and filed hardcopies into secure participant folders.

Data Reliability

All assessments were entered and checked for accuracy by study personnel. Two randomly selected raters from a group of four raters checked administration and scoring of the WAB-R (AQ, LQ, and CQ) on 11% of the total pre- and post-WAB assessments. Inter-rater reliability was high (Cronbach's Alpha = 0.997) with a difference score on the AQ scores to be 1.84 points, CQ scores to differ by 1.57 points, and LQ scores to differ by 1.52 points. Further, sections of the WAB-R including the Spontaneous Speech fluency and content rating scales and the Sequential Commands subtest, were discussed at length among study personnel to create standardized interpretations

and scoring of participant responses. Consensus scoring across three raters was utilized for both of the Spontaneous Speech rating scales for all participants.

Statistical Analysis

Given unequal sample sizes, a linear mixed effects model was conducted on the primary and secondary outcomes. In all analyses, score on the specific test (WAB-AQ, LQ, etc.) was the dependent variable, group (CT-R vs. workbook) and time point (pre-treatment and post-treatment) were the fixed factors, age, and time post-stroke were entered as covariates (unless otherwise noted) and participants were entered as random factors. As follow-up analyses, RANOVAS were performed to further examine treatment-related effects in the two groups.

TABLE 1 | Participant demographic information.

Demographic information	Experimental group	Control group
N	17	15
Age (years)	58.9 (10)	64.2 (9.9)
Sex (female/male)	7/10	7/8
Education (years)	15.8 (2.7)	15.3 (2.5)
Time post-stroke (months)	53.0 (56)	38.1 (32)
Handedness (right/left)	15/2	14/1

Means and standard deviations (provided in parenthesis).

Data Availability

All individual anonymized participant data are provided in **Supplementary Table 1**.

Standard Protocol Approvals, Registrations, and Patient Consents

The study was reviewed, monitored, and approved by Pearl IRB 19-LNCO-102. All participants provided informed consent for this study following procedures described above. This project is registered in the ClinicalTrials.gov registry (NCT04488029).

RESULTS

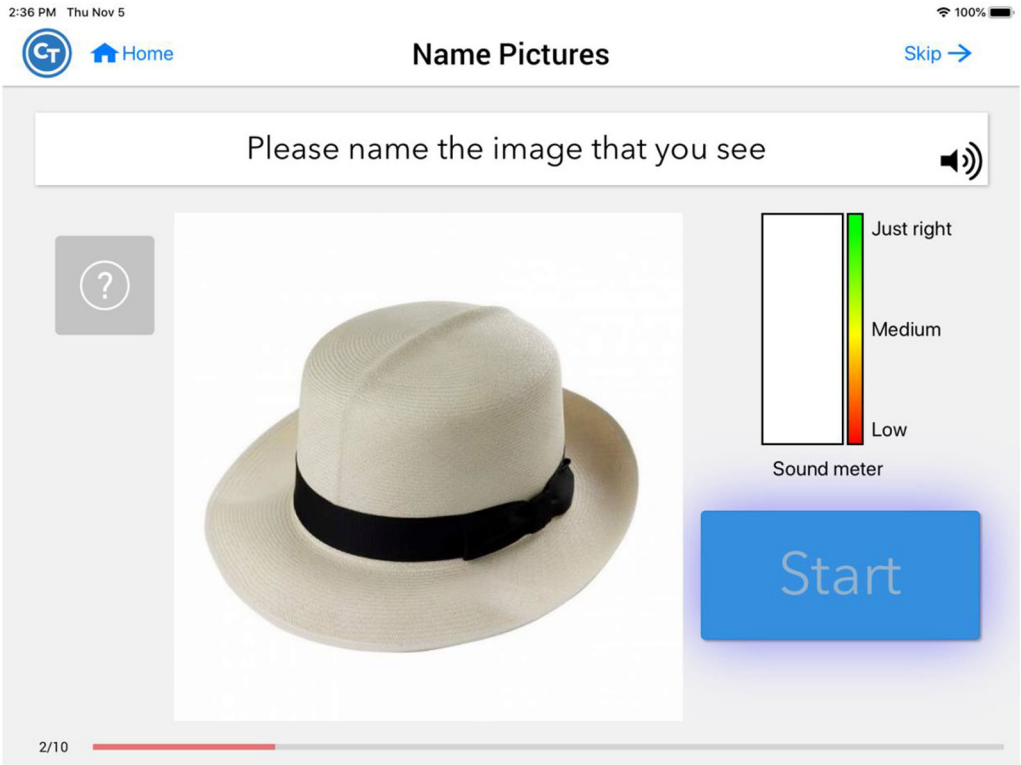
Baseline Measures

Table 1 provides baseline demographic and assessment measures, indicating that there were no pre-existing differences between the experimental ($N = 17$) and control ($N = 15$) groups.

TABLE 2 | Pre-treatment and post-treatment assessment scores for WAB, BTACT, and SAQOL39.

Outcome measures	Experimental		Control	
	Pre	Post	Pre	Post
Western Aphasia Battery, Revised (WAB-R)				
Aphasia Quotient	**61.62 (24.28)**	**68.37 (26.24)**	**66.02 (19.08)**	**66.40 (20.22)**
Spontaneous speech	11.41 (5.33)	12.76 (5.78)	12.40 (3.38)	12.07 (4.01)
Auditory verbal comprehension	155.18 (38.02)	167.24 (33.96)	152.33 (38.78)	156.80 (35.99)
Repetition	50.76 (28.79)	60.88 (29.02)	62.60 (26.85)	66.07 (26.36)
Naming and word finding	65.65 (31.07)	69.71 (32.58)	67.33 (23.13)	66.87 (25.14)
Language Quotient	**64.64 (25.49)**	**69.15 (25.33)**	**66.01 (21.72)**	**66.57 (21.51)**
Reading	70.47 (28.65)	74.47 (23.82)	69.00 (25.13)	70.20 (25.10)
Writing	59.88 (36.73)	58.53 (33.82)	57.90 (32.05)	57.47 (27.50)
Cortical Quotient	**67.69 (22.68)**	**72.38 (23.27)**	**68.81 (18.71)**	**69.59 (19.00)**
Apraxia	49.94 (12.50)	51.71 (11.74)	50.87 (9.50)	50.53 (9.52)
Constructional, visuospatial, and calculation	77.62 (18.68)	79.18 (22.13)	70.20 (17.09)	73.60 (16.66)
Brief Test of Adult Cognition by Telephone (BTACT)				
Immediate recall	2.21 (1.81)	3.15 (1.63)	2.07 (1.44)	2.07 (1.71)
Digit span backwards	2.57 (1.16)	2.71 (1.14)	1.73 (1.22)	2.20 (1.37)
Fluency	9.71 (5.51)	11.43 (6.17)	6.87 (5.11)	8.00 (6.93)
Number series	0.64 (1.15)	0.93 (1.44)	0.33 (0.62)	0.33 (0.82)
Backward counting	10.91 (11.32)	10.93(12.28)	7.27 (10.64)	8.13 (9.78)
Delayed recall	0.71 (1.44)	1.21 (1.89)	1.07 (1.28)	1.20 (1.32)
Stroke and Aphasia Quality of Life Scale−39 (SAQOL-39)				
Mean	3.53 (0.54)	3.77 (0.56)	3.57 (0.58)	3.66 (0.70)
Physical	4.08 (0.70)	4.16 (0.61)	3.92 (0.98)	3.89 (0.95)
Communication	2.70 (0.64)	2.96 (0.71)	2.59 (0.82)	2.74 (0.86)
Psychosocial	3.54 (0.81)	3.81 (0.90)	3.75 (0.54)	3.64 (1.05)
Energy	2.88 (0.97)	3.48 (1.11)	3.54 (1.09)	3.63 (0.91)

Means and standard deviations (in parenthesis).



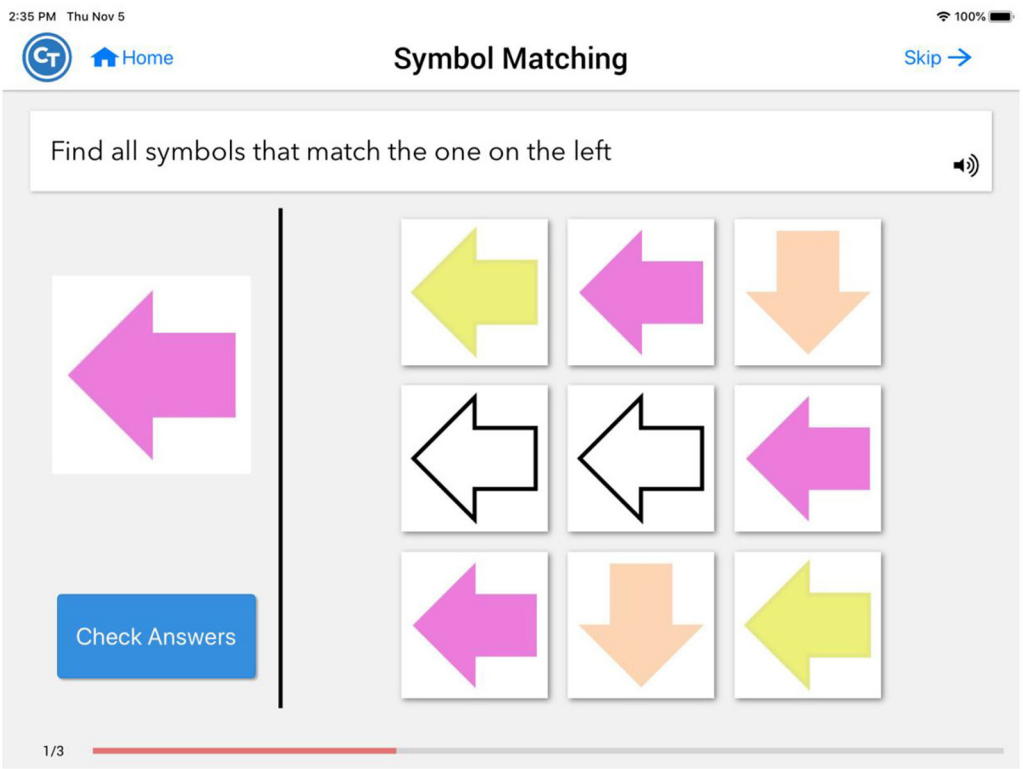


FIGURE 2 | Continued.

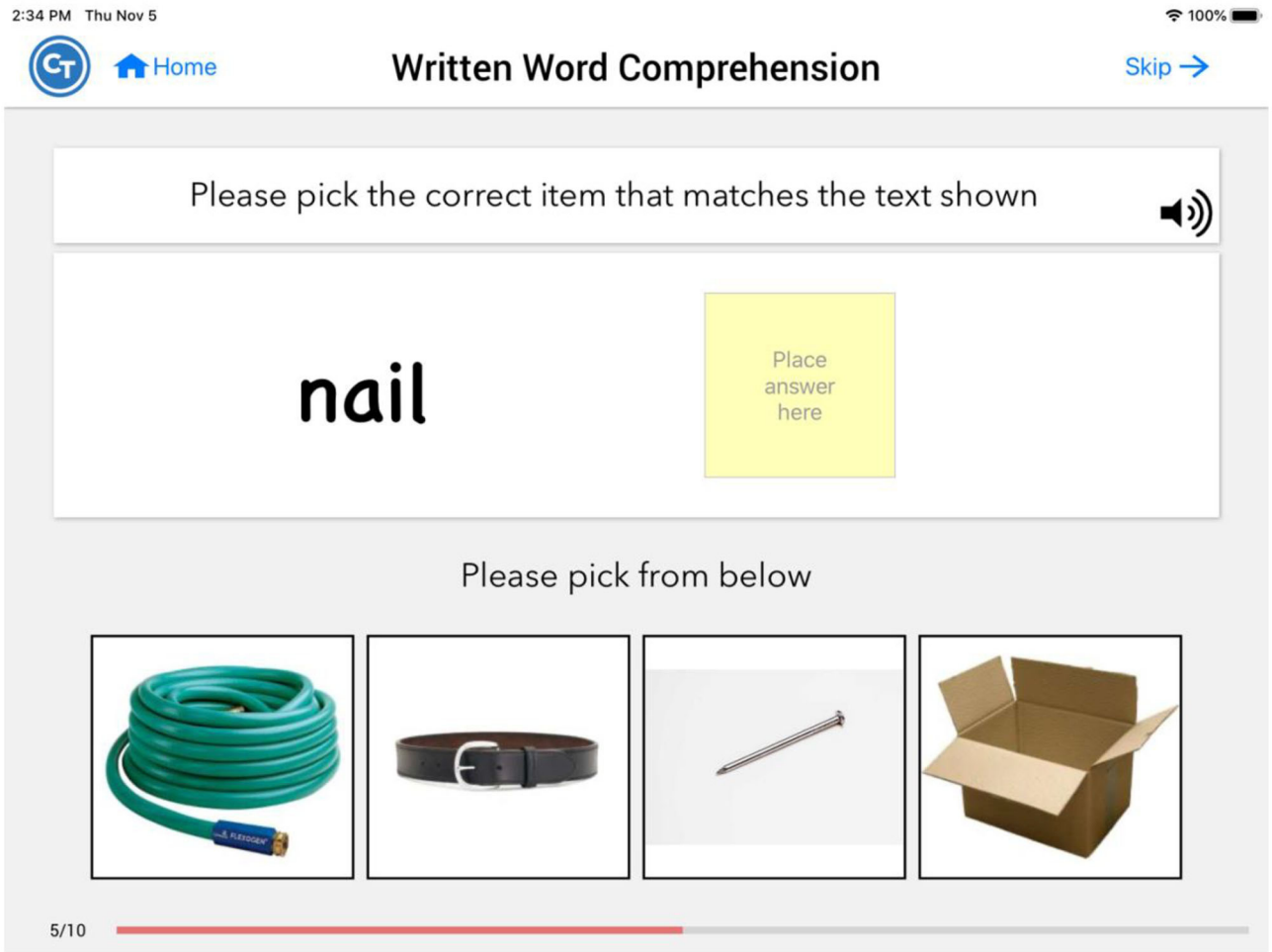


FIGURE 2 | Screenshots of CT-R software.

Further, **Figure 3** provides histogram profiles of specific language and cognitive domain scores from the WAB-R indicating that both groups were similar prior to the beginning of treatment. Additionally, Kruskal-Wallis H-tests were used due to unequal sample sizes showing no difference between the groups on specific variables (age, $p = 0.14$, time since stroke, $p = 0.60$, baseline WAB-AQ, $p = 0.77$).

Primary Endpoint

The primary endpoint in the study was the average change on WAB-AQ. The CT-R group showed a higher mean point change WAB-AQ ($M = 6.75$) than the workbook group ($M = 0.38$). Using a linear mixed effects model, this change was significant at the 1% level. The significant group by time interaction indicated that on average, participants in the CT-R group had WAB-AQ scores of 6.36 points higher than the control group at follow-up than at pre-treatment that was significant ($p < 0.01$, see **Tables 2**, **4** and **Figure 4A**).

Primary Endpoint With Covariates

Even though there were no significant pretreatment differences between the two groups in terms of age, time since stroke and baseline WAB-AQ, controlling for these factors in a linear mixed effects model showed that being in the CT-R group was associated with a 6.43 point increase in WAB-AQ score relative to the workbook group at follow-up than at pre-treatment. Specifically, **Table 4** illustrates that the starting baseline WAB-AQ score was 105.7 (intercept), adjusted by −0.69 for every year of age, and by 0.122 for every month since stroke, participants in the CT-R group had WAB-AQ scores 6.43 higher than the workbook group at the end of treatment.

It is worth noting that the mean differences as a function of treatment for sub scores that comprise the WAB-AQ, were consistently higher for the experimental group than the control group (see **Tables 2**, **4**), including spontaneous speech (CT-R = 1.35, workbook = −0.33), auditory comprehension (CT-R = 12.05, workbook = 4.46), repetition (CT-R = 10.12, workbook = 3.46), and naming (CT-R = 4.05, workbook, −0.46).

TABLE 3 | Description of the intervention per TIDieR descriptions.

Item No.	Item	TIDieR description	
		Experimental (constant therapy group)	**Control (workbook group)**
1.	WHY	Self-management of home-based therapy under remote-guidance could result in an individualized therapy protocol, increased adherence, and compliance of home practice will improve language skills.	Self-management of home-based therapy under remote-guidance without the structured feedback and regimen would result in limited gains.
2.	WHAT materials	Constant Therapy-Research was used as a tailored home treatment program for each participant.	Aphasia therapy workbooks were used for home practice.
3.	WHAT procedures	For each trial in the Constant Therapy-Research software, the participant can select the answer and choose whether to use cues. Once the participant selects the response, immediate feedback is provided regarding accuracy and the participant can proceed to the next trial.	The participant can select pages of workbook to work on for therapy. No feedback is provided on accuracy of attempts on individual items in workbook.
4.	WHO PROVIDED	Speech Language Pathologists or Trained Research Assistants	Speech Language Pathologists or Trained Research Assistants
5.	HOW	Weeks 2 through 8, the experimental group participants completed a video conference check-in with a member of the research staff. During these check-ins, participants were asked to report how often they logged into CT-R to complete their exercises.	Weeks 2 through 8, the control group participants completed a video conference check-in with a member of the research staff. During these check-ins, participants were asked to report how many workbook pages had been completed that week.
6.	WHERE	Participant homes via videoconference	Participant homes via videoconference
7.	WHEN and HOW MUCH	Participants were instructed to use CT-R for at least 30 min a day and at least 5 days a week. CT-R tracked usage of the program.	Control participants were instructed to complete at least 1 exercise within the workbook at least 5 days a week.
8.	TAILORING	Each participant advanced via NPE algorithm using the library of therapy exercises (over 100,000 stimuli within 350+ levels of difficulty spanning 9 different cognitive, speech, and language domains).	Three workbooks with different levels of difficulty were offered to all participants based on participant feedback.
9.	MODIFICATIONS	_____NA_____	_____NA_____
10.	HOW WELL: PLANNED and ACTUAL	CT-R tracks the daily log in times and durations for therapy completion. Biweekly check-ins confirmed study adherence.	Biweekly check-ins confirmed study adherence.

Secondary Endpoints

An additional secondary endpoint was average change on the WAB-LQ. The CT-R group showed a higher mean change ($M = 4.51$) than the workbook group ($M = 0.57$) points. **Table 4** shows that the effects of group, age, time from stroke, and post-treatment (vs. baseline) were not significant. The significant interaction of post-treatment relative to baseline by group, controlling for other variables, was significant, indicating that on average, participants in the CT-R group had WAB-LQ score of 3.97 points higher than the workbook group at post-treatment (**Figure 4B**). Again, mean differences as a function of treatment for subscores of reading were higher for the experimental group (4.00) than the control group (1.20), however, writing scores worsened for both groups (see **Table 2**).

The mean change on the WAB-CQ, showed that the CT-R group showed a higher mean change ($M = 4.69$) than the workbook group ($M = 0.77$). Again, only the interaction of post-treatment relative to baseline by group (controlling for other factors) was significant; participants in the CT-R group had an average WAB-CQ score of 4.01 points higher than the workbook group at the end of treatment (**Figure 4C**). Mean differences as a function of treatment for subscores of apraxia were higher for the experimental group (1.76) than the control group (−0.33), however, mean differences as a function of treatment for subscores of constructional and visuospatial calculation were higher for the control group (3.40) than the CT-R group (1.55) (**Table 2**). Finally, in addition to changes on specific subscores in the WAB, **Figure 5** shows that there were qualitative changes in the aphasia subtypes (as calculated by the WAB) as a function of treatment. Specifically, in the CT-R group, while there were a range of aphasia types prior to treatment, after treatment all participants fell into one of four subtypes (Anomic, Broca's, Conduction, and Within Normal Limits). Contrastingly, the workbook group showed more subtle qualitative changes, and none of them were classified as being within normal limits. Given the small sample sizes of subcategories, no statistical analyses were computed.

In addition to the WAB-R, BTACT, and the SAQOL-39 were also examined (see **Figures 6**, **7**). The mixed effects models for these two measures were not significant for either the main effects or the interaction effects. Therefore, follow-up repeated measures ANOVAs with scores on each of the subtests as the dependent variable, and time (pre-treatment, post-treatment), group (CT-R vs. workbook group), and the interaction between time and group were conducted. **Table 4** reflects all the analyses, the F-ratios and the *p*-values. On the BTACT, only the subtest of verbal fluency showed a significant effect of time, but no significant effects of group or interaction between group and time. On the SAQOL, the overall mean showed a significant improvement as a function of time, as the main effect of group or the interaction between

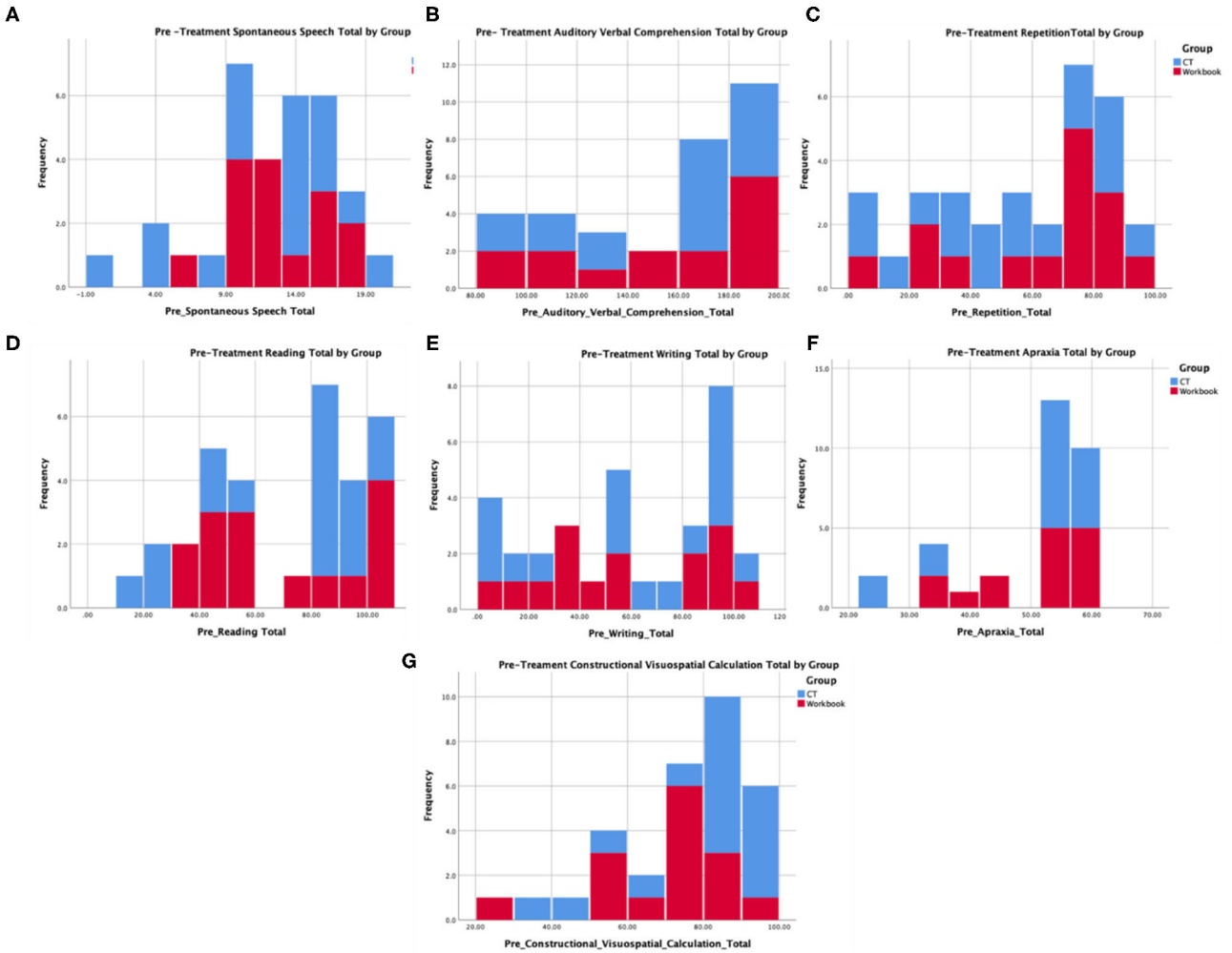


FIGURE 3 | Pre-treatment language and cognitive profiles from the WAB for participants in the experimental and control group that represent **(A)** spontaneous speech, **(B)** auditory comprehension, **(C)** repetition, **(D)** reading, **(E)** writing, **(F)** apraxia, and **(G)** construction, visuospatial, and calculation.

group and time was not significant. Similar results were observed for SAQOL_communication and SAQOL_energy sub-scores, indicating that both groups showed improvements as a function of treatment. The remaining contrasts were not significant.

Finally, to examine the potential influence of demographic variables on the primary outcome measure, bivariate correlations revealed a significant moderate negative relation between age and difference on the post-pre WAB-AQ score ($r = -0.45$, $p < 0.01$), but no significant relation between time since stroke in months and difference on the post-pre WAB-AQ score ($r = -0.07$, $p > 0.05$), and between education in years and difference on the post-pre WAB-AQ score ($r = -0.09$, $p > 0.05$).

DISCUSSION

Currently, standard of care (SOC) for speech therapy involves a stepped approach to rehabilitation in the days, weeks, months, and years following stroke. In general, at each phase following a stroke, there are different SOCs (45). These phases can be described as "acute" (typically the first 24–48 h after a stroke, where the priority is saving a life), "in-patient" (when the patient is recovering, often with medical monitoring, and intense multidisciplinary care), "out-patient" (when living at home but receiving periodic care from healthcare professionals), and "post-discharge" (when no longer under the care of clinical teams). It is in the post-discharge phase that SOC dictates that patients undergo self-directed maintenance. Self-directed maintenance may include the application of learned strategies to daily functional communication exchanges and/or identification of activities or exercises that will allow for practice of the skill area. As noted in the introduction, the state of today's SOC results in the overwhelming majority of patients not receiving the benefit of consistent one-on-one therapy after the first month following their stroke due to structural barriers that preclude extension of traditional one-on-one therapy at a frequency and duration likely associated with optimal outcomes.

TABLE 4 | Statistical analyses for primary and secondary outcomes in the study.

Linear Mixed Model for Primary and Secondary Outcome Measures		
	Coefficient	***P*-value**
WAB-AQ (no covariates)		
Intercept	66.02	**<0.001**
Intervention group (vs. control group)	−4.39	0.59
Post-treatment (vs. baseline)	0.38	0.80
Intervention group* post-treatment	6.36	**<0.01**
WAB-AQ (with covariates)		
Intercept	105.7	**<0.001**
Intervention group (vs. control group)	−9.49	0.26
Age	−0.69	0.07
Time post-stroke	0.12	0.16
Post-treatment (vs. baseline)	0.31	0.84
Intervention group* post-treatment	6.43	**<0.01**
WAB-LQ (with covariates)		
Intercept	108.0	**<0.001**
Intervention group (vs. control group)	−6.83	0.44
Age	−0.71	0.08
Time post-stroke	0.11	0.23
Post-treatment (vs. baseline)	0.53	0.61
Intervention group* post-treatment	3.97	**<0.01**
WAB-CQ (with covariates)		
Intercept	111.5	**<0.001**
Intervention group (vs. control group)	−6.42	0.0.41
Age	−0.72	0.05
Time post-stroke	0.09	0.24
Post-treatment (vs. baseline)	0.67	0.53
Intervention group* post-treatment	4.01	**<0.05**
Repeated Measures ANOVAs for Secondary Outcome Measures		
	f-ratio (error df)	***P*-value**
BTACT		
Verbal Fluency		
Group	2.15	0.15
Time	5.73 (27)	**0.02**
Group* Time	0.239 (27)	0.62
Immediate Recall		
Group	1.79 (26)	0.19
Time	1.36 (26)	0.25
Group* Time	1.36 (26)	0.25
Digit Span Backwards		
Group	2.48 (27)	0.12
Time	3.73 (27)	0.06
Group * Time	1.05 (27)	0.31
Number Series		
Group	1.55 (27)	0.22
Time	1.07 (27)	0.30
Group* Time	1.07 (27)	0.30
Backward Counting		
Group	0.652 (27)	0.42
Time	0.248 (27)	0.62
Group* Time	0.248 (27)	0.62
Delayed Recall		
Group	0.12 (27)	0.73
Time	1.42 (27)	0.24
Group * Time	0.476 (27)	0.49
SAQOL		
Mean		
Group	0.02 (27)	0.88
Time	5.92 (27)	**0.02**
Group * Time	0.886 (27)	0.35
Physical		
Group	0.02	0.87
Time	0.11 (27)	0.74
Group * Time	0.46 (27)	0.52
Communication		
Group	0.63 (27)	0.43
Time	4.33 (27)	**0.04**
Group * Time	0.04 (27)	0.83
Psychosocial		
Group	0.003	0.95
Time	0.15 (27)	0.70
Group * Time	1.35 (27)	0.25
Energy		
Group	1.00 (27)	0.32
Time	8.78 (27)	**0.006**
Group * Time	0.35 (27)	0.06

Bold values are statistically significant.

The present study was the first virtual language/cognitive rehabilitation trial for individuals with post-stroke aphasia. Further, this study joins other recent trials (20) that provide evidence for digitally-based language therapy for post-stroke patients. This Phase II trial showed that individuals who practiced CT-R at home with biweekly check-ins showed an average of 6.43 points greater change on WAB-AQ scores at the end of treatment relative to a control group that practiced workbooks at home and also received biweekly check-ins, even after controlling for age and time post-stroke for participants in the two groups. Importantly, the CT-R group showed a mean improvement of 6.75 points on the WAB-AQ, a change that is above the 5 point threshold for clinically meaningful improvement in speech-language ability (46–48), compared to 0.38 for conventional workbook intervention. Notably, the CT-R group outperformed the control group at the end of the treatment program on WAB-LQ (4.51 points for the CT-R group) and the WAB-CQ (4.69 points for the CT-R group). Changes on the subscores of the WAB subtests were consistently higher for the CT-R group than the workbook group, including on spontaneous speech, auditory comprehension, repetition, naming, reading and apraxia. Interestingly, writing scores worsened slightly for both groups and construction, visuospatial and calculation increased for the workbook group more than the experimental

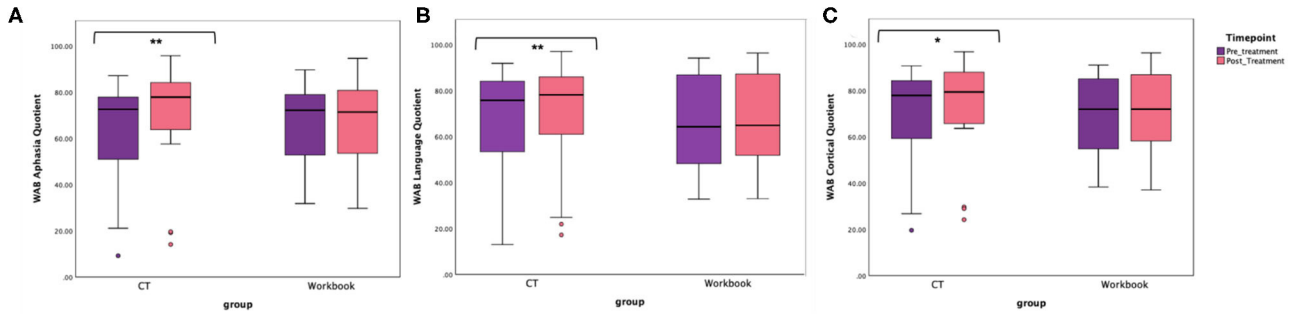


FIGURE 4 | Unadjusted means for WAB-R **(A)** Aphasia Quotient, **(B)** Language Quotient, and **(C)** Cortical Quotient for the two groups (CT-R and workbook) pre-treatment and post-treatment. Significant differences are marked with *. $*p < 0.05$ and $**p < 0.01$.

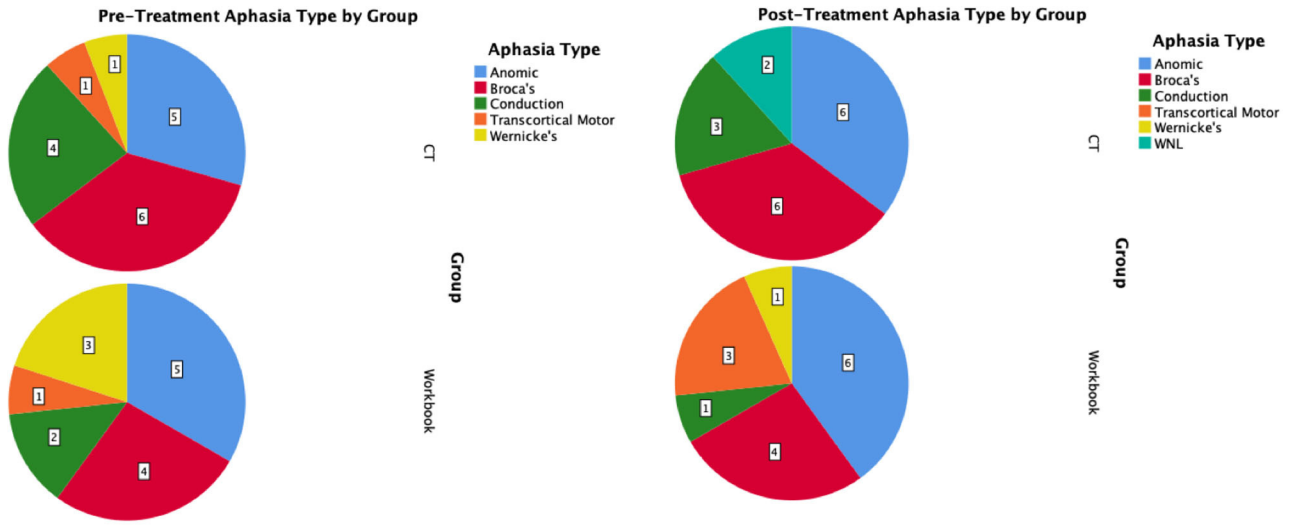


FIGURE 5 | Pre-treatment and post-treatment aphasia subtypes as calculated by the WAB-R shown as pie-charts by intervention group.

group. Decreases in the writing subtests for both groups may be reflective of the reality that CT-R writing practice is done on a tablet and is different from handwriting; and the workbook group may have not practiced writing consistently. It is not completely clear why the workbook group improved more on the constructional, visuospatial, and calculation subtests, but further inspection of participant data suggests that the workbook group improved more on the calculation sections of the WAB. Interestingly, when examining any changes in aphasia subtypes as a function of the treatment, results showed that CT-R made more discernable shifts in their aphasia subtypes, subsequent to improved WAB subscores than the workbook group. Notably, post-treatment, two participants were classified as being within normal limits as per the WAB in the CT-R group, a similar shift was not observed in the workbook group.

Participants in the CT-R group logged into the software program at least 5 days per week, practiced a prescribed number of therapy exercises and received instant feedback on the accuracy for each item. In contrast, the workbook group received physical workbooks to practice, were instructed to practice multiple pages, and importantly, instant feedback was not provided. Therefore, it is possible that the impairment-based drill therapy with feedback targeted in the CT-R software facilitated transfer of similar performance on the domains of language and cognitive function tested by WAB.

Another observation is the difference in the treatment approaches between the experimental and control groups. CT-R was designed to progress the participant through targeted therapy tasks based on their performance. For example, if a participant passed an exercise easily, they would automatically be given a harder task targeting the same skill or domain in the next session. Alternatively, if they appeared to struggle with an exercise, then upon the next login, CT-R would present an easier task targeting the same skill. This automatic calibration of task delivery was designed as part of the software's algorithm with an optional oversight from a study staff. The experimental group, using the CT-R program, also had the added benefit of a study staff being able to manually modify or update their homework program

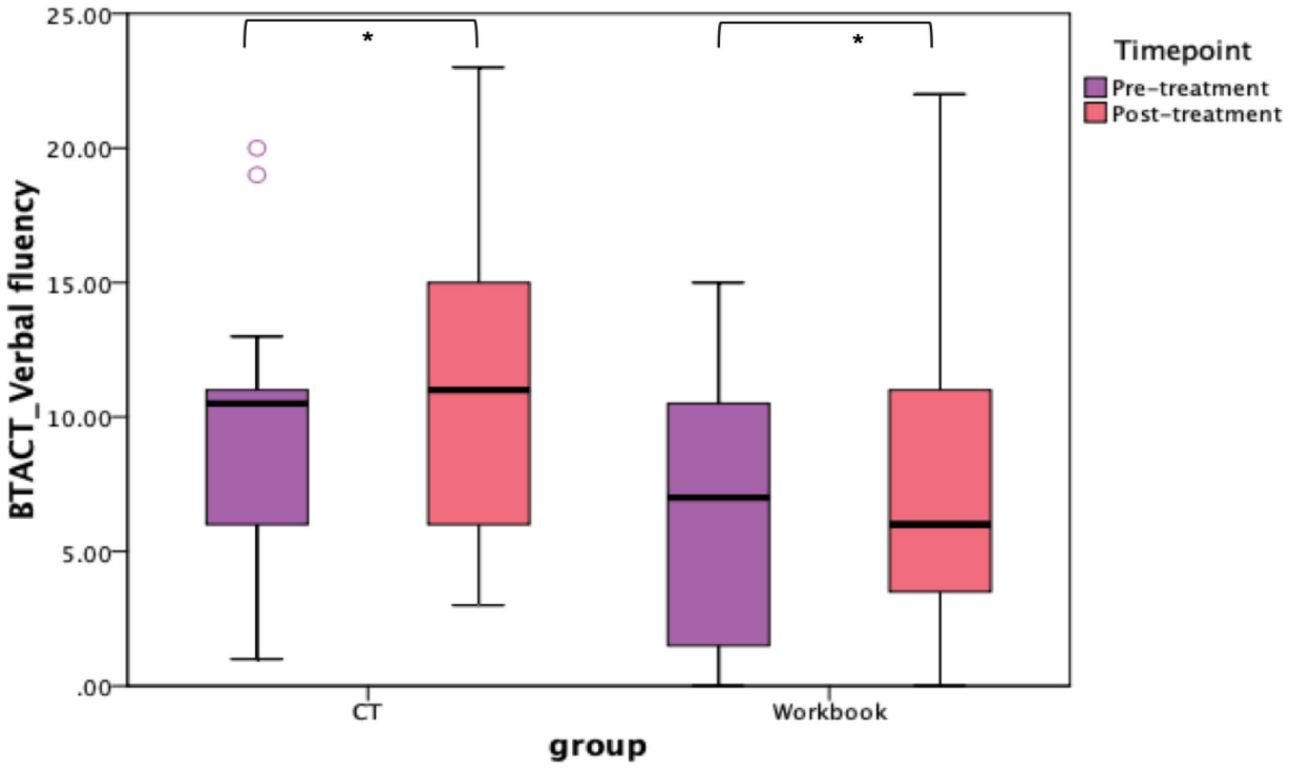


FIGURE 6 | Unadjusted means for BTACT for the two groups (CT-R and workbook) pre-treatment and post-treatment. Significant differences are marked with *. *$p < 0.05$.

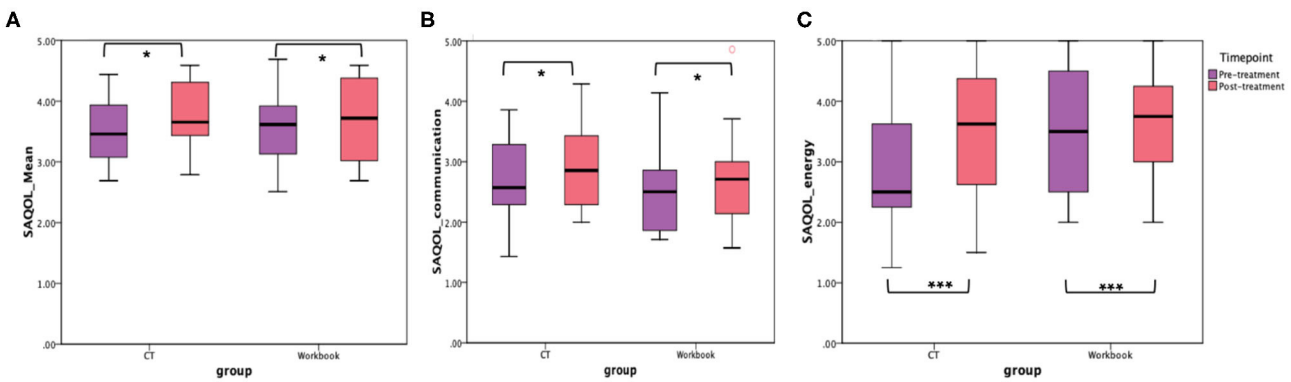


FIGURE 7 | Unadjusted means for **(A)** SAQOL_mean, **(B)** SAQOL_communication, and **(C)** SAQOL_energy for the two groups (CT-R and workbook) pre-treatment and post-treatment. Significant differences are marked with *. *$p < 0.05$ and ***$p = 0.006$.

based on participant feedback. The control group, while using the workbooks could provide feedback regarding the exercises, but could not have the study staff modify, update, or change the homework tasks remotely. These inherent differences in how the treatment program was tailored for each individual participant in the experimental group relative to the control group may have also contributed to differences in the primary outcomes for the two groups.

Compared to the WAB, the critical interaction group by time was not significant for the SAQOL-39 or BTACT in the linear mixed effect models. Instead, repeated measures ANOVAs that compared the two groups as a function of time showed that both the BTACT_verbal fluency and specific SAQOL measures (i.e., SAQOL_mean, SAQOL_communication and SAQOL_energy) improved for both groups as a function of treatment, indicating that participation in the 10 week remote

intervention, independent of the type of treatment, resulted in gains on verbal fluency on the BTACT and quality of life perception on the SAQOL. Apart from the main difference in the mode of therapy exercises practiced, the bi-weekly check-ins with the study staff and the level of flexibility in therapy session practice were identical between the two groups. Therefore, it is possible that the frequent interaction with the study staff who provided feedback about therapy progress and the consequent accountability may have had the same faciliatory effects for both groups. Relatedly, compliance with attendance at bi-weekly check-ins was high across both groups, reinforcing findings that telerehabilitation access decreased missed appointments rates (49). By decreasing barriers due to transportation, commute time, and time out of work, teletherapy provides patients with a more flexible option that ultimately improves engagement with the therapy process. It is important to note that these check-ins were completed completely virtually over videoconference; both as we handle the challenges of COVID-19 and as we look to the future of telepractice, this is encouraging data suggesting that virtual interaction continues to be motivating and engaging for patients.

Nonetheless, the lack of a greater improvement on the secondary outcome measures in the CT-R group vs. the workbook group requires further discussion. It should be noted that the mean difference in the SAQOL-39 ratings for the submeasures ranged from 0.24 to 0.60 (SAQOL_Mean, SAQOL_energy, respectively) for the CT-R group relative to −0.05 to −0.36 (SAQOL_communication, SAQOL_psychosocial, respectively) for the workbook group. These differences for the CT-R group are comparable to 0.33 difference in a study examining the effect of phonomotor treatment on word retrieval (50), hence, contextualizing the gains on this measure in the CT-R group. The BTACT was selected due to its remote administrability, however, there are no studies that report BTACT as an outcome measure for treatment, thus limiting any points of comparison. Additionally, the BTACT requires auditory comprehension and verbal expression, thereby limiting its sensitivity to determine isolated improvements in cognitive function. This hypothesis is further supported by the evidence that participants in the CT-R group increased in the WAB-CQ (a more non-linguistic measure of cognitive function) by 4.97 points higher than the control at follow-up, indicating that improvement in cognitive function was observed by a more non-linguistic measure.

Another interesting but secondary finding of this trial is evidence that PWA can make gains in their language and cognitive skills even in the chronic phase of rehabilitation. While most recovery is expected to occur in the first few months after the stroke (5, 51), this study demonstrates that it is possible to improve language skills in this population even multiple years post-stroke. The average time post-stroke for the participants in the experimental group of this study was 46 months. Yet, there was no significant correlation between time post-stroke and the degree of gains made by patients, indicating that recovery can continue for many years post-stroke. There was a moderate negative correlation between age and improvement on the WAB-R for AQ scores, which does indicate that older patients tended to make fewer gains. Conversely, while some participants were well into their 80's, they were still able to access and manipulate the provided technology, given instruction and support from study personnel, dispelling a common myth that older adults are less able to utilize technology.

While the results from this study are encouraging regarding the implementation of virtual trials, teletherapy as a service delivery model and the use of digital therapeutics like CT-R, there were some limitations to the study. Thirty-two participants were a modest sample size for a study of this patient population, and it is unclear whether these results generalize beyond this study to other similar studies, as well as to other implementations of teletherapy and digital therapeutics. Additionally, there were some practical constraints and barriers to conducting the study. First, as the target population ranged from mild-severe/profound language impairment, it was both critical and necessary for all participants to have a caregiver present during the initial onboarding into the study and pre/post assessments. Nonetheless, even participants with a severe language impairment were able to initiate and complete their homework programs once education and training was provided. Additionally, logistical considerations such as shipping and tracking of materials, and troubleshooting technology, required ongoing time and attention from the study team throughout the trial. Recruitment practices also had to be adjusted to better fit a virtual trial, and instead of the traditional recruitment through a clinical setting, social media and targeted advertising to educate potential participants were implemented recruit them into the study.

While more studies are needed, these results provide encouraging data supporting the efficacy of digitally-based therapeutics, teletherapy, and virtual trial administration. Given that this is the first completely virtual, digital therapeutic treatment study with both assessments and therapy provided remotely, several conclusions can be drawn. First, completely virtual randomized control trials can be performed with checks and balances in place such as weekly check-ins with patients. Second, all the chosen assessments were verified in previous studies for administration in remote assessments and were implementable in a clinical trial. Third, the feasibility of such a trial indicates a novel approach to conduct telerehabilitation studies in an asynchronized format (i.e., participants practice their therapy when it is convenient for them, and without the presence of a clinician) with successful outcomes. Finally, this trial provides evidence that remote assessment and intervention of post-stroke aphasia is both effective and aligned with the ever-shifting needs of how people access care. Participants in this study were located across the United States and Canada and completed the study without issue, suggesting that telehealth services such as these can reduce the geographic challenges that many patients with aphasia face when seeking therapy.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Pearl IRB (19-LNCO-102). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MB, ED, SS, VA, and SK designed and conceptualized study. MB, JP, and SK drafted manuscript for intellectual content. SS drafted and documented IRB protocol. MB, JP, ED, SS, LT, SL, VA, and SK revised manuscript. VA was oversight of technology implementation. MB, JP, and SS were major role in data acquisition. SL was oversight of study conduct, data management, and reporting. JP, SS, LT, SL, and SK analyzed and interpreted the data. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.626780/full#supplementary-material

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Exergaming as Part of the Telerehabilitation Can Be Adequate to the Outpatient Training: Preliminary Findings of a Non-randomized Pilot Study in Parkinson's Disease

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Parkinson's disease is a long-term and progressive degenerative disorder of the nervous system, affecting primarily motor coordination, noticeable as a tremor in one hand. Recent studies reported on positive outcomes of intensive physiotherapy of upper extremities. We built a telerehabilitation system with virtual pick and place tasks for small scale hand movements, and designed a pilot study to find whether such exergaming as a telerehabilitation service provides comparable outcomes as an outpatient exergaming service. A non-randomized pilot trial was designed. Hospital outpatients (28/40) with Parkinson's disease were recruited. Those meeting the inclusion criteria were divided into two groups; seven outpatients were assigned to the home (H) group and 21 outpatients to the hospital (URI) group. Both groups received 10 days of exergaming over the course of 2 weeks, each daily session lasting a maximum of 1 h. Primary outcomes were clinical tests; Box and Blocks Test (BBT), Jebsen Hand Function Test (JHFT), and Unified Parkinson's Disease Rating Scale (UPDRS part III) were carried out before and after the study. Secondary outcomes were hand kinematics and exergaming results; number of successfully moved objects and task time. Statistical analysis was carried out to find significant ($p < 0.05$) differences and Cohen's U3 was used to determine effect sizes. The differences between the groups in gender ($p = 0.781$), age ($p = 0.192$), and duration of the disease ($p = 0.195$) were tested with Bartlett's test and no statistical differences were found with an F test. Both groups demonstrated statistically significant improvements in clinical test UDPRS III ($p = 0.006$ and $p = 0.011$) and the hospital group also in BBT ($p = 0.002$) and JHFT ($p = 0.015$) and with UDPRS III and JHFT even in favor of the home group ($\chi^2 = 5.08$, $p = 0.024$, $\chi^2 = 7.76$, $p = 0.005$). Nevertheless, the exergaming results show significant improvement after training (U3 > 0.86). Exergaming has already been suggested as an effective approach in the planning of rehabilitation tasks for persons with Parkinson's disease. We have prepared a pilot study demonstrating that exergaming at home with telerehabilitation support may provide comparable clinical outcomes. The study shall be followed by a randomized

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study with higher statistical power to provide clinical evidence. Nevertheless, carrying out even part of the rehabilitation program at home is crucial for the development of future telerehabilition clinical services.

Clinical Trial Registration: www.ClinicalTrials.gov, identifier: NCT03175107.

Keywords: perception, Parkinson's disease, exergaming, virtual reality, (tele)rehabilitation, object manipulation

INTRODUCTION

Parkinson's disease (PD) is a slowly progressing degenerative disease of the extrapyramidal system with an unknown cause. The disease often affects people in midlife, between 35 and 60 years of age, with men more likely to become ill than women (1). The main clinical signs of PD are muscle stiffness (rigidity), slowness of movement (bradykinesia), hand tremor, and postural disorders. The disease typically affects the patient's daily activities and thus, their quality of life at different ages. Currently, the degeneration of dopaminergic neurons that trigger changes in the basal ganglia network is treated with levodopa/dopamine (2). However, this may cause a decrease in responsiveness to the medication over time. At the same time, physiotherapy is becoming important in individual treatment of people with PD as they retain more than ¾ of all activities (3, 4). Balance, posture, and mobility related functions often impact the quality of life, as the functions of upper extremities are highly related to participation.

The voluntary activities of patients have proven to contribute to the functional improvement of movement, physical capacity, and other manual activities; balance, walking, reaching, grasping, etc. Exercise based computer games have been introduced to rehabilitation programs (5) and a promising approach seems to be rapidly developing. Several reports on functional progress and performance have been published, but an insufficient number of studies have been dedicated to safety and clinical benefits. Most of the studies have used commercial games for the world-wide public, and those were often found to be too complex (5). Some exceptions also considered safety and functional outcomes (balance, dynamic gait, and quality of life) with commercial outfits (Kinect Adventures™), reported in a feasibility study on positive outcomes (6). Positive effects of computerized cognitive training on several clinical outcomes were examined in older adults (7) and positive cognitive effects of video games have also been reported (8). Most of these studies have been dedicated to postural activities, balance (9), and a large range of motion movements using commercially available "exergames" and motion capture equipment (e.g., Kinect). In spite of the wide-use of commercial motion capture systems at home, the telerehabilitation of patients with neuromuscular diseases or disorders can present a safety issue. Particularly in a standing position, a standing frame is almost essential in (sub)acute stroke rehabilitation (10). Rehabilitation of upper extremities has been successfully implemented; no need for standing frame, no safety issues in the seated position (11, 12) in particular for telerehabilitation (13, 14). However, the majority of neuromuscular disorders may involve spasticity and may require additional passive or even active robotic equipment (e.g., Armeo® Armotion™, Motore++, InMotion Wrist™, ArmAssist®, etc.), most of these are too complex, too expensive, or simply present a safety hazard for independent home use. (Tele)rehabilitation of the upper extremities in persons with PD rarely requires an active exoskeleton, but rather uses exergames (15). For persons with PD, accurate movements such as grasping and fine finger motions may present even more important tasks and may significantly contribute to the improvement of their quality of life, particularly when the medication plan remains unchanged. Such small range of motion tasks are feasible without a robotic device, and make use only of the tracking camera (16), gloves (17), or even electroencephalography (18).

Preliminary studies combining virtual reality technology with physiotherapy in persons with PD and older adults offer promising results (19, 20) in terms of feasibility, but were carried out in a supervised laboratory environment and thus do not provide a sufficient link between motor learning and clinical application. Therefore, we designed equipment specifically for clinical settings. Our goal based small virtual object manipulation task targets hand and finger dexterity in persons with PD (21). Furthermore, the technical solution has been implemented in the experimental telerehabilitation process. Before performing a large-scale study, we carried out an early non-randomized clinical study to check whether participants who had been discharged from hospital and continued treatment at home demonstrated similar clinical outcomes as outpatients without changing the medication plan.

MATERIALS AND METHODS

Study Design and Regulation

An experimental study with patients with PD was designed (**Figure 1**). Participants were included in the study according to the inclusion and exclusion criteria. Baseline clinical assessment was carried out on the day when all participants were still inpatients. On the same day, the patients were discharged from the hospital and allocated to two different groups by selection according to their location of residence and available technical equipment. Both the home (H) group and outpatient (URI) group participated in the post-treatment clinical assessment at the outpatient hospital. Primary outcome measures were clinical tests with questionnaire results as a supplement. Exergaming results were considered to be secondary outcome measures.

(Tele)rehabilitation System

The telerehabilitation system was designed as a client-server model; a server and database running the front-end interface for a therapist working remotely, and client with the exergame, with

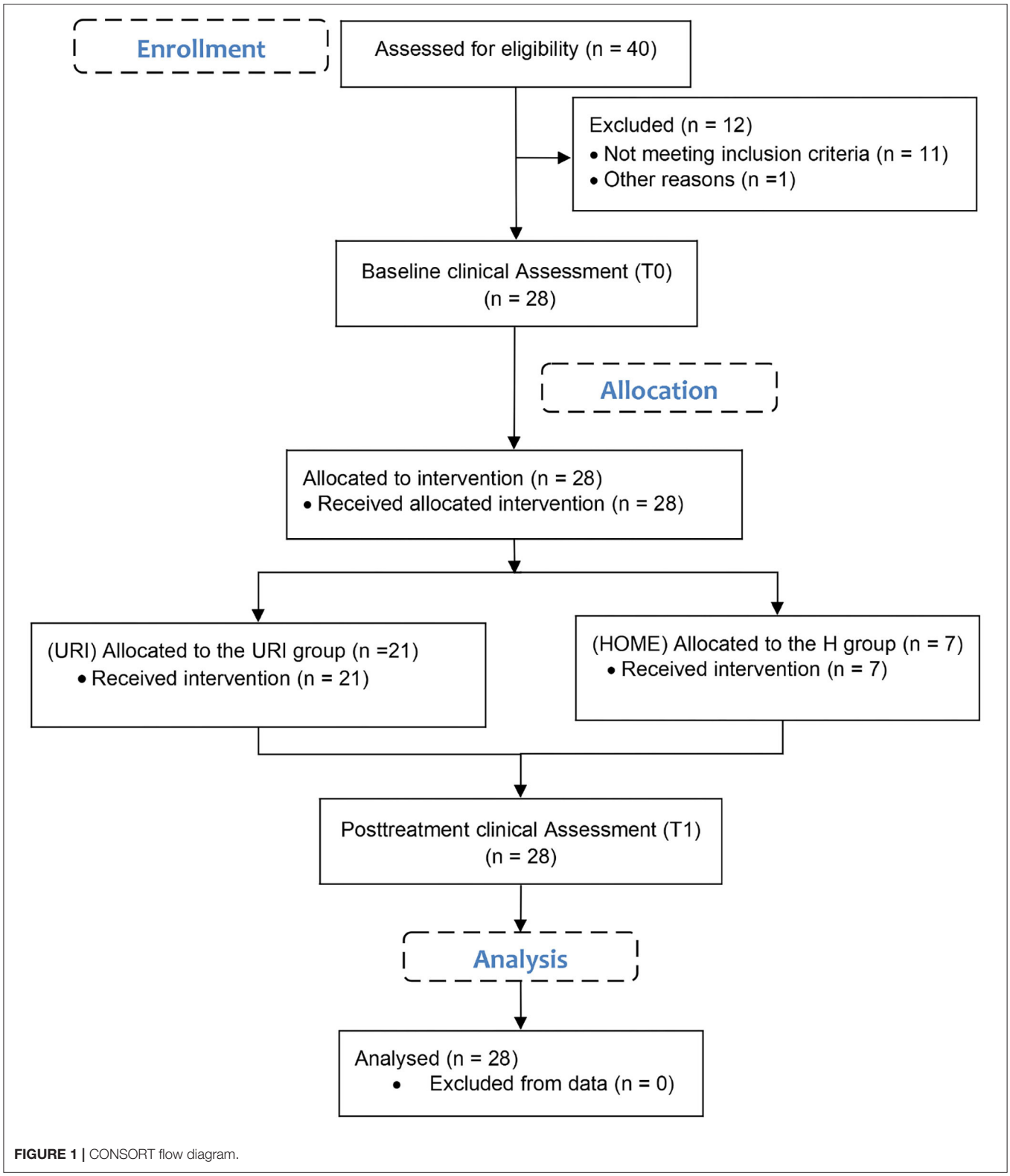

FIGURE 1 | CONSORT flow diagram.

data synchronization occurring after the accomplished session (16). The client software was running on the bare-bone computer (Intel NUC i7, Win10 OS) and was designed and programmed in the Unity3D (Unity Technologies, CA, USA) environment. The designed virtual environment (VE) consisted of a simulated grass floor, hidden reflecting walls, and a model of a treasure chest on the left for right-handed or on the right for the left-handed participants. We placed 10 virtual cubes of various colors in

the VE, but the same physical model (weight, bounce stiffness, material, and size) to ensure repeatability of the process.

The interaction object with the VE and the virtual object was a real hand-sized virtual model of the participant's hand (left or right). The participants could see the projection of their real hand and fingers as an avatar, a model of the metal hand. The kinematics of the virtual hand were adequately similar to the movement of the real hand and fingers. The movements of the real extremity were tracked by a small, mouse-sized infrared camera (Leap Motion Controller—LMC, Leap Motion Inc., CA, USA), that can detect 3D hand movement as well as the movements of fingers. The camera connects to the high-speed USB 3.0 port of the computer and requires a suitable graphic adapter (e.g., Nvidia GeForce series). The infrared camera requires light calibration or constant light conditions to operate properly with the pre-calibrated settings. The control software was written in C# using the LMC libraries within the MonoDevelop open-source environment (22). The assessed parameters were used to calculate the participant's performance. The recorded time and number of cubes placed successfully into the virtual chest were displayed to inform the participant about their performance. All parameters, including the hand kinematics, were simultaneously recorded on the local computer as an ASCII (*.txt) file and later sent to the remote server (**Figure 2**).

10Cubes game (**Figure 2**): The goal of the exergame was simple. Pick up and place 10 cubes, one by one into the open treasure chest within 2 min. One cube at a time should be picked up with a pincer grasp. If the participant completes the game before the time elapses, they receive a time bonus. If not, then the number of collected cubes counts as the final score.

Participants

Twenty-eight persons (12 males and 16 females) with PD participated in the study. All participants were initially involved in the same rehabilitation program at the hospital. Inclusion criteria comprised: (a) Parkinson's disease or Parkinsonism with functional disorders in the upper extremities and minor problems with daily activities; (b) participants at level 2–3 according to the Hoehn and Yahr Scale (23). All tests were performed in the morning about 1–2 h after taking the medication to assure equal conditions for all participants. The recruited participants were divided into two groups according to their place of residence and the technical capabilities of their home:

- Seven patients in the home (H) group; three males and four females, 62.3 ± 7.3 years old, seven had the right side affected, with a duration of PD 5.8 ± 2.5 years.
- Twenty-one patients in the outpatient hospital (URI) group; nine males and 12 females, 69.5 ± 5.8 years old, three had the left side affected, 18 had the right side affected, and one had both sides affected, with a duration of PD 6.4 ± 4.5 years.

The study was approved by the local ethics committee and all participants provided a written consent for the publication of any potentially identifiable images or data included in this article.

Research Protocol

The participants of the URI group were comfortably seated in front of the 22″ computer screen placed on a table. The LMC was placed on the desk in front of the participant (see **Figure 2** right). Window blinds were used to assure appropriate constant lighting conditions. The participants of the H group were asked to sit comfortably in front of the 22″ monitor or 32″ TV screen and put the LMC on a small even surface above the subject's knees in order to cover the optimal working space (see **Figure 2** left).

A skilled occupational therapist explained the goal of the study and the procedure of the task to each of the participants at the start of session zero (the trial session at the hospital). The therapist or the participant him(her)self-started the application, if computer skills allowed. The participants of the H group managed the application by themselves or were provided assistance by a relative or a caregiver.

The goal of the task was to pick up and place 10 small virtual cubes lying around the virtual environment into the open treasure chest by the more affected hand. If both or neither of the hands were affected, then the participant would use his/her dominant hand. For the purpose of the study, the model of virtual cubes used the same weight, material, and bouncing factor of the cubes and light conditions.

The participants of both groups were involved in the identical protocol. Differences in environment and equipment were unavoidable among the home participants. Each participant received 10 training therapies with the 10 Cubes exergame over the course of 2–3 weeks. Each session lasting ∼30 min (max. 1 h) with breaks. Within the session, participants managed to accomplish the 10 Cubes task five times. Short breaks of 1–2 min between the trials were compulsory.

Before commencement of the sessions, the participants received a baseline clinical assessment. The clinical tests UPDRS motor function part (24), Jebsen Hand Function Test (25), and Box and Blocks Test (26) were carried out. All participants took the same tests at the post-treatment clinical assessment. All clinical tests were carried out by a skilled occupational therapist.

Data Assessment

Clinical Outcomes

The clinical test Box and Blocks Test (26) is a low cost standardized rehabilitation measure that assesses unilateral gross manual dexterity. It is intended for evaluation of daily living activities, coordination, and dexterity of upper extremities. The participant moved blocks one by one from one compartment to another in 60 s. The outcome of the test was equal to the number of blocks, with more blocks indicating better function.

The Jebsen Hand Function Test (25) is a comprehensive rehabilitation measure test for uni-manual hand functions for the assessment of daily living activities. It comprises of seven sub-tests for dominant and non-dominant hands (writing a letter, card turning, picking up small objects, stacking checkers, stimulated feeding, moving light and heavy objects). The sub-tests measure speed, not the quality of movement. The outcome of each sub-test is the time taken to complete the task. Total score is the sum of times, with a lower score indicating better function.

FIGURE 2 | Participants at exergaming in home (left) and hospital (right) environment. Both groups used the same 10Cubes game and LMC. The telerehabilitation system for the home group recorded the data locally and transferred afterwards to the server.

The UPDRS (24) is a tool for general assessment of Parkinson's disease. We used only the motor function part III in the study in order to assess speech, facial expression, tremor at rest, action tremor of hands, rigidity, finger taps, hand movements, rapid alternating movements of hands, and actions related to balance and posture. Each point is graded from 0 (no impairment) to 4 (severe impairment). Therefore, a higher score indicates greater disability and zero points indicates the absence of disability.

After the study, the participants were asked to fill out the 39-Item Parkinson's Disease Questionnaire (PDQ-39) (27). However, we considered the results with precaution (28).

Exergaming Results

The kinematics of the hand were tracked by the LMC and analyzed online by computing the position of the cubes and determining the (un)successfully handled cubes, and monitoring the remaining time and offline analysis of the entire hand kinematic (22). The observed outcomes were the number of successfully picked and placed cubes and the remaining time.

Sample Size Considerations

We set the confidence level to 95% in order to keep the average clinical value within expected limits. With an expected 10% margin of error and a population size of 40, we estimated that 29 participants would be required for the preliminary non-randomized study.

Statistical Data Analysis

Differences between the H group and URI group in terms of gender, age, and duration of the disease were statistically checked for equal variances and normal distribution with Bartlett's Test and compared with an *F*-test (Matlab, MathWorks Inc., Natick MA, USA). Mean values and standard deviations were computed for the number of cubes and remaining time for each of the 10 sessions/days. Additionally, the statistical differences between the 1st and 10th sessions were tested with the Kruskal-Wallis Test, a non-parametric method. The significance level was set to $p = 0.05$. Matlab Statistical Toolbox (MathWorks Inc., Natick MA, USA) was used to manage and transform data, and to calculate the statistics. Effect sizes were determined with Cohen's U3 (29) analysis with the Measures of Effect Size (MES) Toolbox (30). The U3 defines the proportion of data from one group that were smaller than the median values of the other group. There was no effect at U3 = 0.5 and maximal at 1 when all group data at post-assessment were above the median of the data at baseline or 0 when all group data were below the median of the data at baseline (effect size: small 0.4/0.6, medium 0.3/0.7, and large 0.2/0.8).

TABLE 1 | Analyzing differences between the home (H) group and hospital (URI) group.

Variable	URI group	H group	Bartlett's test (χ^2/p)	*F*-test (*p*-value)
Gender (M/F)	9/12	3/4	0.025/0.875	0.781
Age (mean/SD)	69.48 (5.78)	62.29 (7.32)	0.522/0.470	0.192
PD (years)	6.38 (4.48)	5.83 (2.48)	2.026/0.155	0.195

Clinical tests were statistically examined separately for the H group and URI group. Data obtained in both groups were tested for normality and equality of variances with Bartlett's test. If the homogeneity of variances test did not fail (χ^2, $p < 0.05$), we used the Student's *t*-test to compare the means of the clinical baseline and post-assessment. We hypothesized that clinical tests related to small object manipulation with hands or fingers can demonstrate statistically significant progress for both groups. Additionally, the effect sizes were examined by Cohen's U3. The statistical differences of the mean values between the H and URI groups were tested with the Kruskal-Wallis Test.

RESULTS

Participants Characteristics

All 28 participants entering the study accomplished the 10 sessions according to the protocol and completed the assigned baseline and post-treatment clinical tests. The statistical test does not reject the null hypothesis that the variances in gender, age,

TABLE 2 | Results of the clinical tests in both groups at baseline and post-treatment.

	Hospital URI group				Home (H) group				Interaction	
	Baseline		Post		Baseline		Post		Kruskal-Wallis	
Test	Mean	SD	Mean	SD	Mean	SD	Mean	SD	χ^2	*p*-value
BBT	44.6	9.3	49.1	9.8	52.9	12.9	56.6	13.6	3.38	0.066
UPDRS III	31.2	10.9	28.8	10.9	24.6	6.3	22.9	7.3	5.08	0.024*
JHFT	67.7	24.4	63.2	25.9	50.8	13.5	44.5	9.8	7.76	0.005*
	Bartlett's	*T*-Test	Cohen's		Bartlett's	*T*-Test	Cohen'			
	χ^2/*p*-value	*p*-value	U3	CI [x-y]	χ^2/*p*-value	*p*-value	U3	CI [x-y]		
BBT	0.052/0.820	0.003*	0.57	−7.37	0.017/0.896	0.204	0.42	−10.09		
UPDRS III	0.0001/0.997	0.005*	0.33	0.77	0.110/0.739	0.011*	0.43	0.55		
JHFT	0.066/0.797	0.068	0.26	−0.38	0.559/0.455	0.015*	0.29	1.70		

$p < 0.05$ statistical significant difference.

and duration of the disease are equal across H and URI groups (**Table 1**).

Clinical Outcomes

The variances of the clinical tests at baseline and post-assessment were tested with Bartlett's test ($\chi^2 < 1$, $p > 0.05$) and the equal variance *t*-test was used to test the data. Significant improvements of function were found after the training with at least two clinical tests (**Table 2**). The URI group improved their score for all three clinical tests, BBT, UPDRS III, and JHFT, at post-assessment (**Figure 3**). The mean differences in the BBT and the UPDRS III were also statistically confirmed with $p < 0.003$ and $p < 0.005$, respectively. In the H group, improvements of function were found with all three tests, but changes were statistically significant for UPDRS III ($p < 0.011$) and JHFT ($p < 0.015$). The analysis of the effect sizes showed medium (U3 = 0.33) to large (U3 = 0.26) changes in JHFT, while changes in BBT scores were small in the H and URI groups (U3 = 0.43, U3 = 0.57, respectively) at post-assessment.

The statistical differences in clinical scores between the H and URI groups were tested with the non-parametric Kruskal-Wallis Test for interactions due to unequal sample sizes. The JHFT and UPDRS III indicated significant differences ($\chi^2 = 7.76$, $p = 0.005$, $\chi^2 = 5.08$, $p = 0.024$, respectively) of means between the H group (mean 44.5 vs. 50.8 s, 22.9 vs. 24.6 s) and the URI group (mean 63.2 vs. 67.7 s, 28.8 vs. 31.2 s) as shown in **Table 2**.

Figure 4 shows the outcomes of the seven sub-tests for the dominant/affected hand (writing a letter—WAL, card turning—CARDT, picking up small objects—SOP, stacking checkers—STCHK, stimulated feeding—STFEED, moving light objects—MLO and moving heavy objects—MHO). Both groups achieved lower scores (improvement) at post-assessment. Larger changes can be noticed for the H group, particularly in the sub-tests that require small object manipulation (MLO, WAL, SOP).

The 39-Item Parkinson's Disease Questionnaire (PDQ-39) was filled by seven participants from the H group. The participants in general had severe difficulties with mobility, body discomfort, and also with emotional well-being (**Figure 5**). They did not feel stigmatized or lack of social support. The participants managed activities of daily living.

Exergaming Results

The participants of both groups have improved their exergame score, particularly the number of successfully placed cubes (**Figure 6**). The performance of the H group was also much faster, with more than 25 s remaining at the last session. All changes were substantially large (Cohen's U3 > 0.814). The URI group did not manage to save extra time (U3 = 0.5), however, some individuals in this group performed faster and saved up to 70 s (**Figure 6**).

The mean values between the H and URI groups were different for collected cubes as well as for the remaining time at post-assessment. The statistical differences between the groups were shown by the Kruskal-Wallis test (**Table 3**) for cubes (interaction, $\chi^2 = 24.62$, $p = 6.98{*}10^{-7}$) and remaining time (interaction, $\chi^2 = 11.33$, $p = 0.0008$).

DISCUSSION

Safety, usability, and the patient's perception, particularly of telerehabilition, are major challenges of using novel technological solutions and methods in rehabilitation. The primary goal of telerehabilitation has always been the safety of participants. Technical safety is nowadays not questionable (Medical Device Regulation, 2020/561) (31), but rather acceptance, feasibility of the approach in remote or home environment, and clinical evidence. This may present a challenge in gait and balance training (32) but feasible and promising for the rehabilitation of upper extremities, particularly in the seated position. The patients improve the range of motion, grip muscle strength, coordination, movement velocity, and fine and gross dexterity. They can use non-immersive serious games or virtual reality and contactless measuring equipment (33). The gaming approach is often found to be motivating and challenging for patients, while game diversity and fun is of great importance (34). Fernández-González et al. reported on promising results using the LMC in

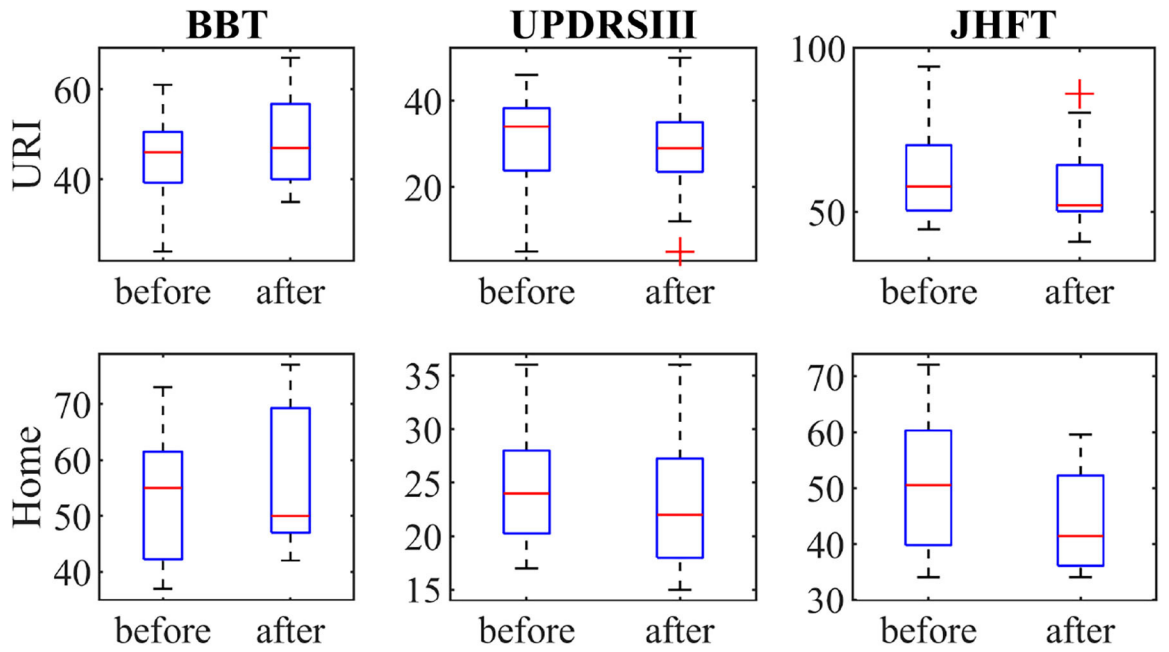

FIGURE 3 | The outcomes of the clinical tests Box and Blocks Test (BBT), Unified Parkinson's disease rating scale (UPDRS) part III, and Jebsen Hand Function Test (JHFT) for the home and hospital (URI) groups before the commencement of the training and post-assessment.

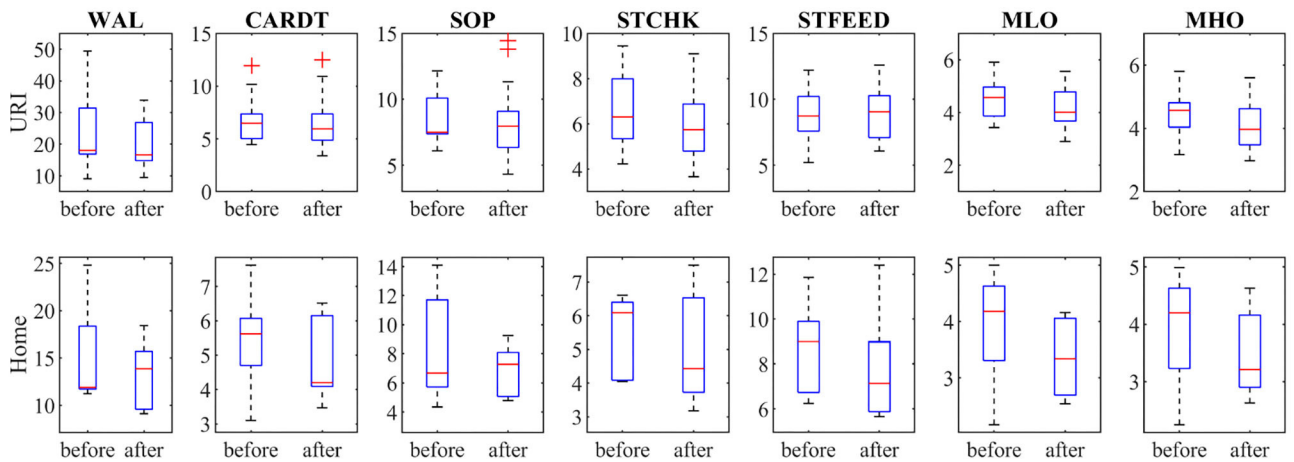

FIGURE 4 | Shows the outcomes of the seven sub-tests of the Jebsen Hand Function Test for dominant/affected hand (WAL, writing a letter; CARDT, card turning; SOP, picking small objects; STCHK, stacking checkers; STFEED, stimulated feeding; MLO, moving light; MHO, moving heavy objects).

patients with PD in the randomized control study. Significant improvements with clinical tests were observed despite the small number of participants. Our findings with a larger hospital group are in accordance with the reported results. The patients significantly improved their Box and Blocks Test score with dominant/more affected hand and UPDRS III scores using similar equipment with the virtual pick and place task. A substantial improvement (Cohen's U3 = 0.26) of JHFT outcomes was reported, but the statistical test showed marginal differences ($p = 0.068$). Insight into the sub-tests demonstrates progress with moving light objects, picking up small objects, and writing a letter. Further improvements in other sub-tasks would require additional exergames targeting different movements, cognition, and perception (35). The home group achieved a lower score in the moving light objects and picking up small objects sub-tasks and statistically significant improvement after the training ($p = 0.015$). The reason for better performance can be found in other sub-tests, i.e., writing a letter and stimulated feeding, the various tasks they usually do at home. The home group showed mean functional improvement of fine movements and gross manual

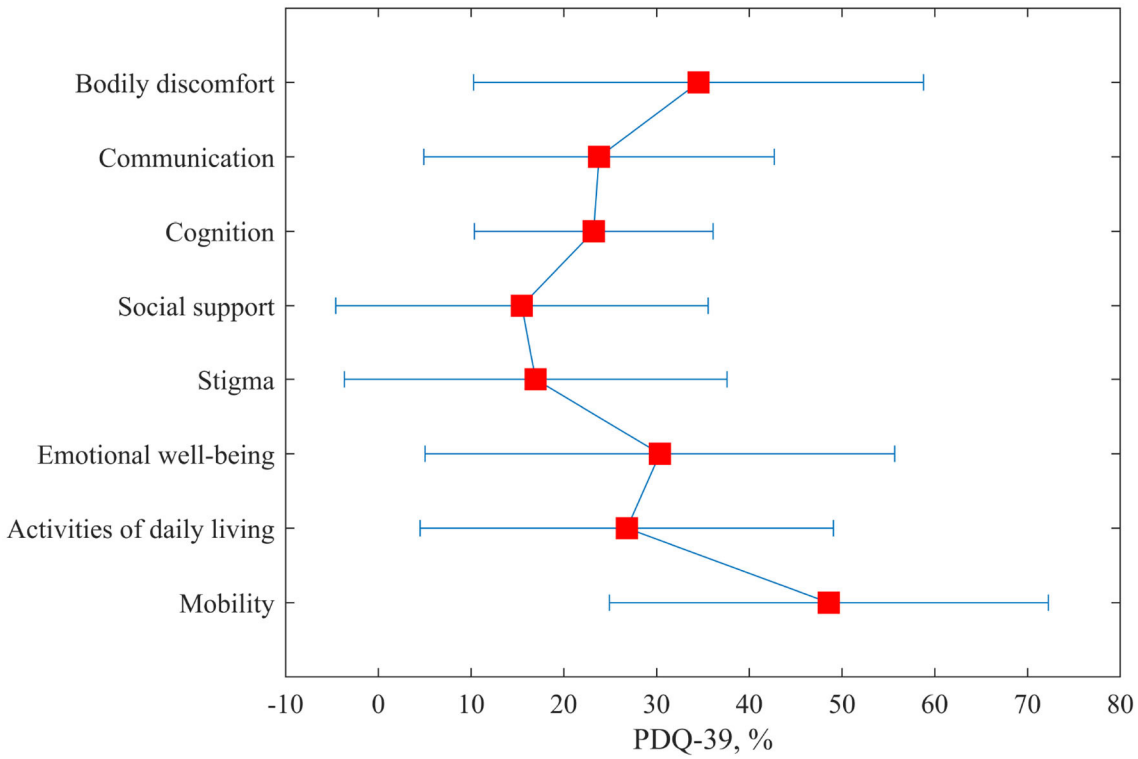

FIGURE 5 | The outcomes of the Parkinson's Disease Questionnaire (PDQ-39) for the home group only.

dexterity with BBT, but statistically insignificant due to the high dispersion and small sample size.

Both groups of participants substantially improved their game scores and managed to save extra time. In fact, the home group was successful in gaming and their mean remaining time at the end of the trial was more than 25 s, meaning that the members of this group mastered the game. On the other hand, we have noticed that seven patients in the hospital were even better and two patients hardly managed to complete the game. This resulted in a great variation of results and may suggest that some patients have a more impaired pinching function than others. Also, the home group may have improved the response time of fingers to a stimulus quicker through the sessions (35). Even if we assume that the home group performs more physical reality tasks than the hospital group, Wang et al. demonstrated comparable outcomes with the virtual reality tasks (19). Visual motion stimuli contributed to the improvement of movement speed in persons with PD in the short-term. Recently, researchers (36) have demonstrated quantitatively positive results for upper extremities with immersive virtual tasks also using the LMC. Significant improvements of strength, fine and gross coordination, dexterity, and speed of movement were shown. The findings on comparable outcomes with the physical world lead to the validation of fully-immersive VR Box and Blocks Test (37). The authors suggested that virtual BBT could be used as a reliable indicator and may be accepted by clinicians and patients. However, the outcomes of our previous randomized control study show that there is no functional difference between immersive and non-immersive virtual tasks, except motivation (21). Motivation (38) could have an important impact on final results in both groups, home and hospital.

Exergaming as Telerehabilitation Service

The LMC has previously been integrated into the home virtual rehabilitation system for stroke survivors (39). The system comprised simple goal oriented tasks for finger flexion/extension, wrist movement, and reaching with changing difficulty levels. The outcomes demonstrated improvement of upper extremity function and increased intrinsic motivation level. The participants maintained motivation for 12 weeks which could have an important impact on adherence and motor outcome. Motivation in chronic stroke can also be maintained by multi-user exergames (40). The outcomes of a study with Kinect™ (Microsoft, Inc., USA) suggested that the participants spent more time in multi-user training and achieved a higher Fugl-Meyer Assessment of Motor Recovery After Stroke Upper Extremity score. An interesting approach to involve active participation was the use of electroencephalography as neuro-feedback to control the interaction with the system (18). Such equipment can also be used for monitoring, despite the fact that the don and doff as well as the operation may present a technical issue for patients at home. Our study is focused on persons with PD who may not experience spastic movements and functional progress due to the progressive disease. However, the core of

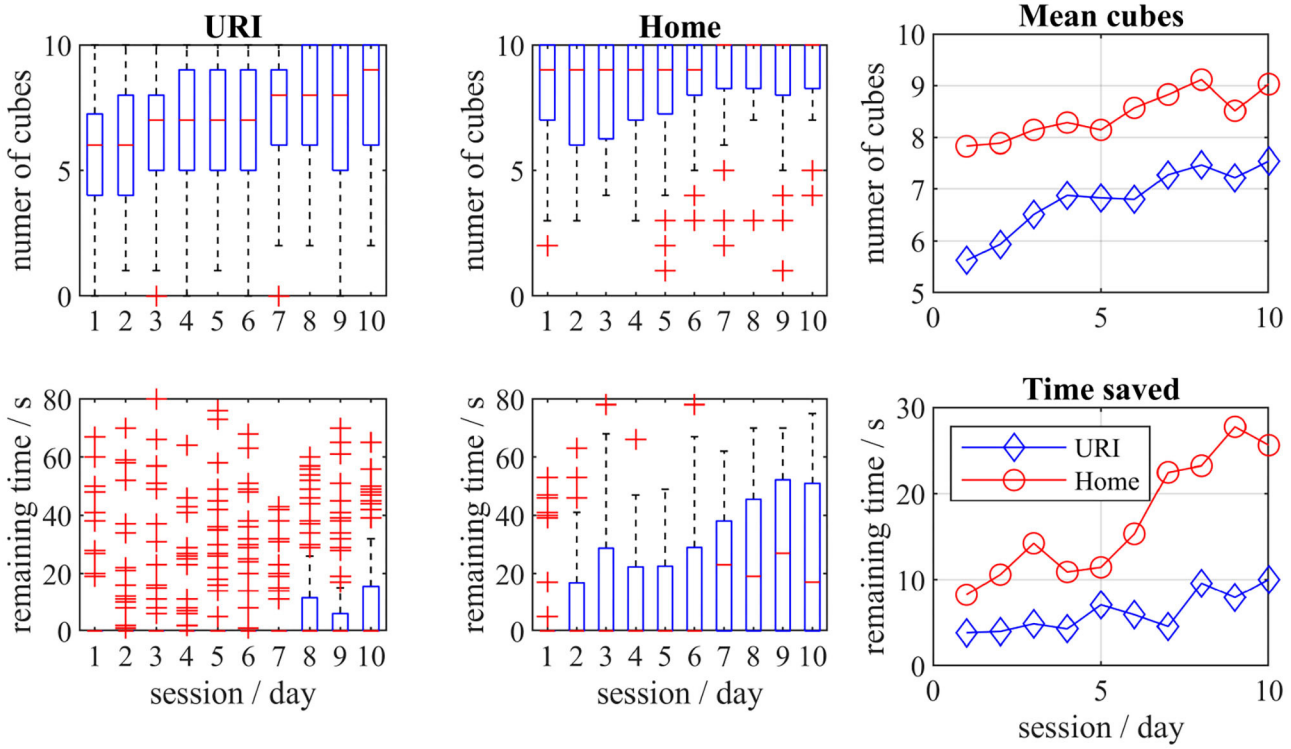

FIGURE 6 | The boxplots for the number of successfully placed cubes and the remaining time for home and hospital (URI) groups. The mean values for both groups per sessions are also presented.

TABLE 3 | Statistical differences between the hospital (URI) group and the home (H) group in exergaming.

Variable	Cohen's U3		Kruskal-Wallis	
	URI group	H group	χ^2	*p*-value
Number of cubes	0.867	0.857	24.62	0.00007*
Remaining time	0.500	0.814	11.33	0.0008*

Additionally, the effect sizes (Cohen's U3) for baseline and post assessment is shown.
**p < 0.05 statistical significant difference.*

our telerehabilitation exergaming was in accordance with recent developments and studies; exergaming should be motivating, easy to use, and demonstrate comparable clinical effectiveness as the training in the hospital.

Limitations

The system was designed as an easy-to-use, simple tool and does not require any special knowledge or technical skills. Despite simplification with a design devoid of an additional user interface for settings, it was not an easy task for the participants with PD to run the application. Data loss was prevented by saving them locally then uploading to the server afterwards.

We have noticed that successful collection of cubes before the elapsed time sweeten the pot. However, we are aware that the game score cannot be of relevant information for the clinician, but rather a good indicator of participant motivation/effort. We could also have applied the intrinsic motivation inventory to both groups (41).

The recruited number of patients of this mean age would have been enough for the estimated statistical power (0.8) with alpha set to 0.05. They could have been randomized into two groups, even 10 participants per group would have made the two independent sample study possible. Unfortunately, not all patients were eligible for the trial and we ended up with only seven who were capable of handling the technology. Although we found significant differences in outcomes across the groups with medium effect size, the small sample size in H group is a limiting factor. Consequently, there is a high risk of bias. A non-negligible factor would be the lack of motivation, ability to perform required exercises, poor sensibility or muscle tone.

Hereby, we suggest a randomized clinical trial, possibly multi-center to provide clinical evidence. Results can also be supported with the intrinsic motivation inventory to assess the patients' psychological behavior.

Implications for Prospective Studies

The aim of this preliminary non-randomized study was to demonstrate that the location of supplemented occupational therapy is marginal and that the telerehabilitation approach may significantly change such therapy programs in the future. However, as the study did not provide sufficient clinical evidence,

prospective randomized clinical trials in telerehabilitation settings are essential.

CONCLUSION

The telerehabilitation system was initially designed for the proposed study; simple virtual reality task for small range of motion and precise manipulation, without specific user interface, short term evaluation protocol, and easy-to-use hardware and software. Indeed, small and precise movements are important and valuable for the daily life activities of persons with PD. Such activities increase participation and may potentially influence the progress of PD. The outcomes of the pilot study demonstrated comparable clinical outcomes indicating that part of the occupational therapy can be provided as telerehabilitation service. A limitation of such studies is often the small number of eligible participants. However, the COVID-19 pandemic and continuous pressure on rehabilitation centers have irrevocably altered the approach, the technology and its digital adoption for health care professionals and patients.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Materials**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The study involving human participants was reviewed and approved by Ethics Committee of University Rehabilitation Institute, Republic of Slovenia (Approval Number: 13042015). The procedure was in accordance with the principles of the Declaration of Helsinki on biomedical research on human beings, the provisions of Council of Europe Convention on the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine (Oviedo Convention) and the principles of Slovenian Code of medical ethics. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

IC lead the research, made the analysis, and wrote the main structure of the manuscript. AH and DZ carried out the occupational therapy and clinical assessment, the participants selection, and coordination. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.625225/full#supplementary-material

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frontiers in Neurology

ORIGINAL RESEARCH
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Telemonitoring of Patients With Chronic Traumatic Brain Injury: A Pilot Study

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Telehealth systems have shown success in the remote management of several neurological disorders, but there is a paucity of evidence in disorders of consciousness (DOC). In this study, we explore the effectiveness of a new telemonitoring system, for monitoring Vegetative State (VS) and Minimally Conscious State (MCS) patients. This was a prospective, mono-center randomized controlled study. We included only traumatic brain injury (TBI) patients who required long-term motor/cognitive assistance having a stable clinical condition. We examined their clinical evolution over ∼4 years of the follow-up period. Twenty-two TBI patients were enrolled and equally divided into two groups: one telemonitored at home with our service and the second admitted to a standard long-stay hospitalization (LSH) program. Patients enrolled in the telehealth service (age: 49.9 ± 20.4; 45% female; diagnosis: 36% VS/64% MCS) were demographically and clinically-matched with those admitted to the LSH program (age: 55.1 ± 15; 18% female; diagnosis: 54% VS/46% MCS). Thirty-six percent of patients in the LSH program died before completing follow up evaluation with respect to 18% of death in the group of TBI patients telemonitored at home. At follow-up, patients in LSH and telemonitoring groups showed similar clinical progression, as measured by CRS-r, NCS, WHIM, and LCF scales, as well as by the number of medical complications (i.e., bedsores, infections). Finally, we estimated the total daily cost per patient. Severe TBI patients enrolled in the conventional LSH program cost 262€ every single day, whereas the cost per patient in the telehealth service resulted to be less expensive (93€). Here, we highlight that our telehealth monitoring service is as efficacious as in-person usual care to manage a severe neurological disorder such as TBI in a cost-effective way.

Keywords: telerehabilitation, traumatic brain injury, medical complications, healthcare costs, coma recovery scale revised

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INTRODUCTION

Traumatic brain injury (TBI) is one of the leading causes of death and disability worldwide. Annually, over 2 million incidents are causing traumatic brain injury (TBI) and while research is continually accumulating to better understand the trajectory of clinical course, treatment options lag (1). Recovery from TBI is a complex process and severe brain injuries commonly result in a wide range of disorders of consciousness (DOC). This condition is characterized by high heterogeneity

in clinical phenotypes and, mainly, in prognostic models (2–4) that contributed to disappointing results in several clinical trials (5).

Functional recovery following TBI usually reaches its peak at around 6 months and begins to decline as soon as 1 year after the neurological event (6). Generally, the vast majority of patients receive high-quality care and support in intensive neurorehabilitation unit (IRU) and are discharged successfully back to their communities. However, a significant minority of patients often continue to suffer from limited independence and face very long stays in rehabilitation wards that are far from their homes and families (7). Long-term hospitalization (LSH) is generally required for unstable TBI patients, although there is pressure to manage patients outside of the hospital in order to reduce costly hospital resources. Thus, there is a need for new post-discharge programs that may support families in caregiving, fostering, at the same time, better functional status and reducing healthcare service access, hospitalization, and costs.

One promising avenue to answer this need is telerehabilitation. As recently stated by the World Federation for NeuroRehabilitation (http://wfnr.co.uk/), telerehabilitation can be divided into different levels: (a) from the basic intervention of telecounselling and telecare; (b) passing from telemonitoring (with physiological data recorded by wearable devices); (c) until to teletherapy (where patients underwent specific treatments for improving clinical status). Overall, after several years of studies, telerehabilitation is considered an important tool for improving health and quality of life in neurological patients living in nursing homes, and potentially reducing healthcare hospitalization, service access, costs, finally reducing the caregivers' burden (8, 9).

In older adults with multiple chronic conditions, Takahashi et al. (10) demonstrated that telemonitoring was effective in reducing hospitalizations and physician visits when compared with usual care. In patients with Parkinson's disease (PD), it has been shown that telerehabilitation is feasible, well-received by patients and caregivers, even in more severe disease states (11). Outcomes are also similar between telerehabilitation and usual in-person care. In particular, Beck et al. (12) revealed no worsening of clinical outcomes in PD patients, including a number of emergency room visits, hospitalizations or level of caregiver burden in patients undergoing a telerehabilitation intervention with respect to patients enrolled in a usual care group requiring hospitalization. Finally, the experiences of AD-related telerehabilitation programs have demonstrated several advantages mainly in increasing the number of physician visits, in reducing the distance traveled by caregivers and in time spent traveling (11, 13). Considering long-term outcomes, Kim et al. (14) compared individuals who received their dementia care through video-based visits conducted at a clinic and who received their dementia care at the university hospital. They found no significant difference in cognitive decline (measured with MMSE score) between the two groups over 2 years of follow-up.

Despite telehealth systems have shown success in remote management of several neurological disorders, there is a paucity of evidence in DOC. The aim of this study is to determine the effectiveness of a new telehealth follow-up program for patients with TBI, which ensures h24 high level of assistance with multi-parametric vital sign monitoring, and periodic neurological and neuropsychological teleconsulting. We specifically examine the efficacy of this management strategy, by comparing long-term clinical outcomes of chronic TBI patients with respect to another demographically and clinically matched group of TBI patients admitted to a usual LSH program.

MATERIALS AND METHODS

Participants

The study was realized on patients with severe brain injuries who required long-term motor/cognitive assistance, consecutively enrolled at the time of their transfer from the IRU to LSH period, within the S. Anna Institute (Crotone, Italy). The evaluation for enrollment in this study was performed at admission in long-term care. The inclusion criteria were: (1) diagnosis of acquired TBI according to neuroradiological and clinical assessments; (2) patients having a stable clinical condition; (3) absence of infections; (4) age range 18–75 years; (5) availability of receiving in-home rehabilitation service; and (6) availability of a home internet connection. Exclusion criteria were: (1) cardiorespiratory instability; (2) high-risk of spontaneous fractures; (3) presence of other severe pathologies influencing the outcome; (4) refusal by the caregiver of the patient's home transfer.

The study was approved by the Ethical Committee of the Central Area Regione Calabria in Catanzaro, according to the Helsinki Declaration. The surrogate decision-makers of the patients enrolled in the study provided their written informed consent. The original forms were collected and stored. All the experimental procedures were conducted according to the policies and ethical principles of the Declaration of Helsinki.

Design and Procedure

This was a mono-center randomized controlled study, evaluating the clinical evolution of severe TBI patients after ∼4 years intervals from admission in two different long-term care facilities (LSH or telemonitoring).

From January 2012 and December 2015 all patients admitted in LSH after discharge from IRU were evaluated to identify the subjects fulfilling the inclusion and exclusion criteria, who entered the study. From January 2012 and December 2019, the enrolled patients were prospectively studied.

The study procedure included four steps: (1) baseline assessment; (2) group assignment; (3) long-term care observation period; (4) follow-up assessment. In the first stage, the eligible TBI patients underwent a clinical examination at baseline. In the second stage, participants were randomly assigned to the 2 groups (LSH or telemonitoring) using a computer-generated, site-stratified, randomization schedule. Randomization was stratified according to age and sex. For each stratum, random numbers were assigned to the participants and put into envelopes; it was determined randomly whether the even or odd number would enter the LSH group. Participants were assigned to the study according to the numbers they received on opening the envelopes.

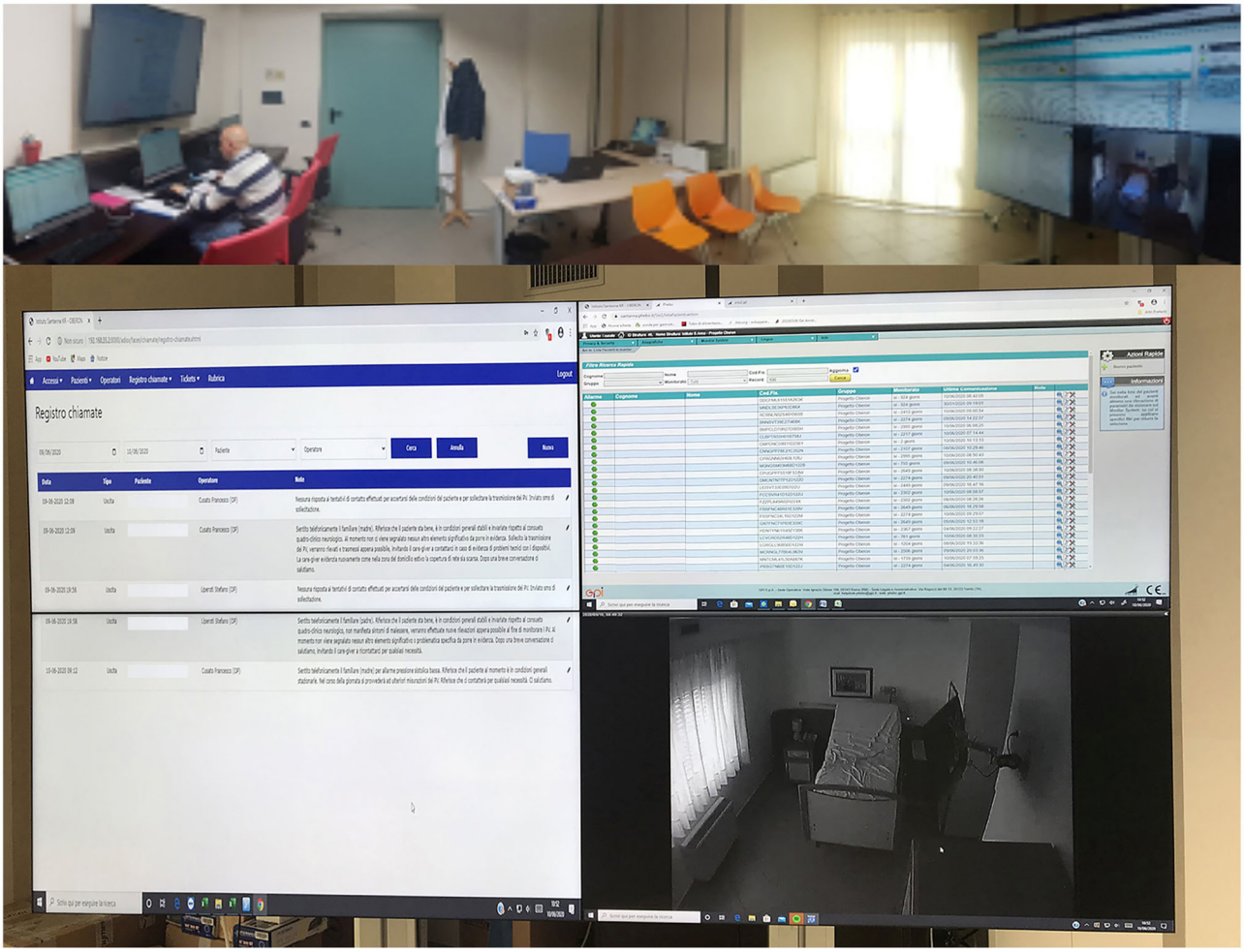

FIGURE 1 | Advanced videoconferencing telehealth system for controlling neurological patients at-home.

After the randomization (T0), the patients allocated in the telemonitoring group were transferred at home where they were remotely monitored by a real-time interaction service, while those assigned to the LSH group continued the medical care in the hospital. The different steps in this process were administered by different research assistants who were blinded to the other processes.

Finally, after ∼4 years intervals (T1), patients from both groups were given a blind evaluation, using the same protocol as at baseline. Length of stay was extracted from charts and electronic records. This variable was defined as the time interval (in days) from the time of the discharge from IRU to the time the consultation was completed.

Caregivers enrolled in the telemonitoring in-home service underwent several training sessions. Methods used include hands-on training, staff modeling of techniques, and supervised family- led overnight stays in a transitional living apartment. Caregivers were instructed to coordinate follow-up telehealth encounters with the telemedicine center via secure messaging and to upload physiological measurements during the post-discharge phase.

Outcome Measures

Neurological examination was performed by 2 skilled physicians who monitored the emergence of medical complications administrating the following clinical scales at admission and after the follow-up period: the Revised Coma Recovery Scale (CRS-R) (15), the Wessex Head Injury Matrix (WHIM) (16); the level of cognitive functioning as measured by the LCF (17) and the Nociception Coma Scale (NCS) (18).

Telehealth System for Clinical Monitoring

This system is designed for patients in VS and MCS, and their families. The program is funded at an acute medical level of care to treat primary and secondary conditions and provide continuous skilled nursing (24 h/d, 7 d/wk) for monitoring all basic care activities. Patients received a monthly consultation either by a neurologist or a psychologist. Members included a

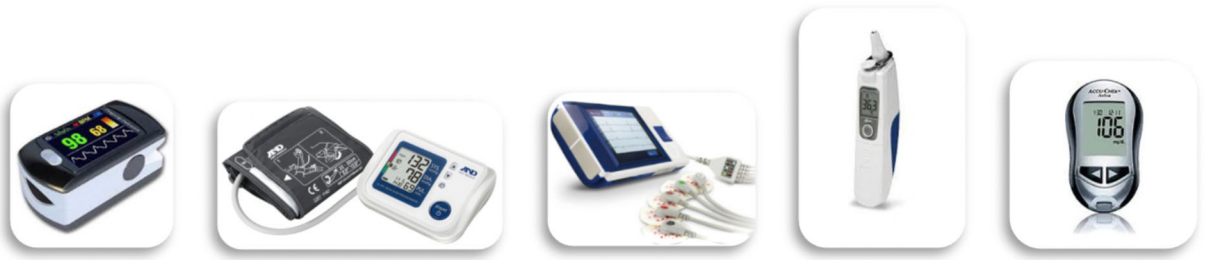

FIGURE 2 | Medical devices included in the telehealth service for assessing physiological measures of patients at-home.

physiatrist, physical therapist, respiratory therapist, occupational therapist, neuropsychologist, and family counselor. All team members are responsible for monitoring patients for signs of diminished functioning, physiological changes, infections, bedsores, new or worsening symptoms.

The clinical monitoring was delivered with an advanced videoconferencing system, whereas the patients provided with low-cost monitoring devices, able to collect data about his/her health status. All treatments are based on scheduled videoconferences between the patient's home and the Clinical Units, so that the therapist can always control and modify the exercises (**Figure 1**). The technological device of the assistance service, dedicated to people with DOC, has been designed to manage a service center called SOU (Special Operating Unit), capable of managing real-time information generated by home and mobile workstations supplied by healthcare workers. The entire software design and architecture was built for devices running into the Android operating system, whose applications are Java-based. The Android technology was used for satisfying these particular needs:

— Operating System designed for mobile devices
— System Flexibility
— Open Source
— Kernel-based on "Linux Kernel"
— Using the Dalvik Virtual Machine to run Dalvik dex-code which is translated from "Bytecode Java" code

The solution implemented is a medical software classified as a class III (certified 93/42/EEC). The device allows us to manage video assistance services, acquisition and transmission of vital physiological parameters (e.g., pressure, glycemic rate, weight, ECG, SpO2, heart rate, etc.), questionnaires and multimedia files (e.g., image of bedsores, etc.).

The operation center has three fixed stations with diversified access for each operator registered to the system. The home workstations provide for the use of a smartphone that acts as a gateway and a series of devices connected via Bluetooth technology. App installed on the smartphone generates a visual and sound massage, at predefined intervals by the care plan, through which users are invited to measure the physiological parameters provided by the plan itself. The measurement is carried out with the devices included in the home kit delivered to the caregivers and is guided by audiovisual support through the same App.

During the monitoring at home, the patients used wearable monitoring devices to monitor their status and to provide real-time feedback. The physiological parameters provide a measurement of the heart rate, pressure, saturimetry, temperature and glycemia (in the case of diabetic subjects) (**Figure 2**). These data are transmitted in real-time on the platform that compares them with the alarm thresholds defined (by an algorithm of artificial intelligence) during the creation of the medical record and based on the patient's history. The platform then returns through a color code (red/green) output to the operator present in the SOU. If an alarm occurred, the internal management procedure is activated opening the contact between the SOU and the patient's home via video call. The video call in the current home configuration is made through a portable PC and all clinical data were stored in a cloud-based system localized at S. Anna Institute for further evaluation and statistical purposes.

The entire care model is defined by 15 procedures with over 120 operating instructions and in April 2018 this obtained the UNI EN ISO 9001:2015 Certification.

The LSH program consisted of standard care focused on the treatment and prevention of secondary conditions of the primary nervous system, cardiovascular, respiratory, digestive, musculoskeletal, and skin origin. The program is adjusted in reason of the clinical needs. As for telemonitoring service, team members in the LSH program are responsible for monitoring new or worsening symptoms during the hospitalization stay period.

We also performed a cost analysis to compare our home-based, telemonitoring system to clinic-based medical assistance. The prices of all resources identified were estimated from the hospital's perspective (taking into account the proportions of public/private Italian hospitals in 2019). Costs were totaled across the 1-day treatment period and compared to clinic-based long-term assistance.

Statistical Analysis

Statistical analysis was performed using SPSS software (version 26; Statistical Package for Social Sciences; www.spss.it). Assumptions for normality were tested for all continuous variables. Normality was tested using the Kolmogorov–Smirnov

test. The analysis for differences in clinical and demographical variables at admission was made by using Chi^2. Considering the small sample size, non-parametric statistics (Mann–Whitney U-tests and the Wilcoxon signed-rank test) were applied in order to analyze the effects of group and intervention. For all tests, a $p < 0.05$ threshold was considered to be statistically significant.

RESULTS

Clinical Data

Among an initial cohort of 264 DOC patients, twenty-two TBI patients fulfilling all criteria were included in the study.

Patients enrolled in the telemonitoring program (age: 49.9 ± 20.4; 45% female; diagnosis: 36% VS; 64% MCS) were demographically and clinically matched with those admitted to LSH program (age: 55.1 ± 15; 18% female; diagnosis: 54% Vegetative State VS; 46% MCS) (**Table 1**). The presence of percutaneous endoscopic gastrostomy (PEG) (81 vs. 72%, in LSH or telemonitoring programs, respectively) and of tracheostomies (54 vs. 27%, in the telemonitoring and LSH programs, respectively) were similar between the two groups (**Table 1**).

At ∼4 years follow-up evaluation, patients of both groups showed similar clinical progression. Thirty-six percent of patients in the LSH program died before completing telehealth follow-up evaluation with respect to 18% of death in the other group (**Table 2**). Similarly, considering the evolution of medical complications during long-term chronic cure, the number of bedsores (18 vs. 0%, in the LSH or telemonitoring programs, respectively) and infections (36 vs. 18%, in the LSH or telemonitoring programs, respectively), showed a tendency to a lower number of complications in telemonitoring group, but these differences weren't significative (**Table 2**). Considering neuropsychological measurements, we did not find any significant difference between groups, although patients enrolled in the telemonitoring program showed better CRS-r and NCS-r scores in the follow-up period with respect to baseline (**Table 3**).

Finally, we estimated a total daily cost per patient in order to quantify the economic impact of the telehealth system with respect to hospitalization. The mean total cost per patient in the LSH group was 262€, whereas in the telemonitoring group cost was approximately 93€. The different components of cost are shown in **Table 4**. The major component of cost for the LSH program was human resources focused on staff time dedicated to patient care, whereas for telehealth program approximately half of the health costs relied on the equipment (i.e., medical devices) (**Table 4**).

DISCUSSION

In this study, we provide preliminary evidence about a new telehealth service useful to monitor patients with DOC, secondary to TBI. Overall, we showed that in a wide temporal window (4 years), the clinical condition of disease was similar in a group of demographically and clinically-matched patients admitted in a traditional LSH program with respect to telemonitoring service. Indeed, we found the maintenance of a stable and similar: (a) cognitive status (as measured by the CRS-r and LCF scales); (b) level of responsiveness to the environment (i.e., pain stimulation) (as measured by the WHIM and NCS scales); and (c) occurrence of medical complications (i.e., bedsores, infections). Moreover, our data confirm the cost-effectiveness of our system, since we found that delivering assistance by telemonitoring is less expensive than providing the same service in the hospital.

Despite no significant difference was detected in all clinical evaluations, it could be highlighted that patients telemonitored at home showed a trend toward a better clinical picture (**Table 3**). Our telemonitoring service allows us to organize remote treatments by means of videoconferences made by the clinicians with the caregiver/family, answering every question about the clinical condition, observing the progression of medical complications and suggesting how to prevent them. This service is useful to guide caregivers in different steps of treatment relative, for instance, to the management of complex medical complications, such as tracheostomy and route of feeding, as well as bedsores. Furthermore, the daily monitoring of vital signs and the phone contact between caregivers and the telehealth operators allowed the family to consider their relatives involved in a "protected" room like the hospital, avoiding feelings of

TABLE 1 | Demographic and clinical data at admission.

Variables	Long-hospital stay group	Telemonitoring group	*p*-level
Number	11	11	
Sex (% female)	18%	45%	0.13§
Age (years)	55.1 ± 15 *51 (29–79)*	49.9 ± 20.4 *44 (21–85)*	0.39*
Length of stay (d)	1,330 ± 751.7 *1,218 (418–2,968)*	1,560 ± 805.3 *1,675 (500–2,486)*	0.12*
Diagnosis	54% VS 46% MCS	36% VS 64% MCS	0.39§
Tracheostomy (yes, %)	54%	27%	0.24§
PEG (yes, %)	81%	72%	0.61§

*Data are shown as mean ± SD and median (range). VS, Vegetative State; MCS, Minimally Conscious State; PEG, Percutaneous endoscopic gastrostomy. *Mann–Whitney U-test; §Chi^2.*

Data expressed as median (range) are reported in italic.

TABLE 2 | Medical complications in TBI patients during follow-up period enrolled in the two long-term care programs.

Variables	Long-hospital stay group	Telemonitoring group	*p*-level
Bedsores (yes %)	18%	0%	0.13
Infections (yes, %)	36%	18%	0.33
Death (yes, %)	36%	18%	0.33

§Chi^2.

TABLE 3 | Clinical outcome of TBI patients at admission and after follow-up.

Variables	Long-hospital stay group	Telemonitoring group	Long-hospital stay group	Telemonitoring group	Statistical analysis (*p*-level)			
					Between group*		Within group§	
	Baseline	Baseline	Follow-up	Follow-up	Baseline	Follow-up	Long-hospital stay group	Telemonitoring group
CRS-r	9.2 ± 3.8 *8.5 (4–16)*	10.8 ± 5.1 *10 (4–21)*	9.2 ± 5.1 *8 (4–19)*	12.4 ± 6.1 *11 (4–23)*	0.48	0.31	0.99	0.08
NCS	4.9 ± 2 *4 (3–9)*	5.8 ± 2.9 *5.5 (2–10)*	4.9 ± 2.5 *4 (2–10)*	6.3 ± 3.9 *6 (2–11)*	0.44	0.22	0.91	0.06
WHIM	20.5 ± 14.2 *18.5 (7–41)*	18.1 ± 12.2 *19 (3–53)*	22.5 ± 19.3 *17.5 (7–60)*	14.3 ± 8.4 *16 (3–25)*	0.65	0.29	0.71	0.33
LCF	2.4 ± 0.5 *2 (2–3)*	2.6 ± 0.5 *3 (2–3)*	2.6 ± 1.1 *2 (2–5)*	2.5 ± 0.5 *2.5 (2–3)*	0.35	0.81	0.31	0.99

Data are shown as mean ± SD and median (range). CRS-r, Coma Recovery Scale-revised; NCS, Nociception Coma Scale; WHIM, Wessex Head Injury Matrix; LCF, level of cognitive functioning.

**Mann-Whitney U Test.*

§Wilcoxon W test.

Data expressed as median (range) are reported in italic.

TABLE 4 | Components of daily health care costs.

Sub-components	Long-hospital stay group	Telemonitoring group
Nursing and Staff time (€)	116	25
Medication (€)	23	10
Hospitality (€)	90	0
Equipment (€)	30	48
Internet Connection (€)	0	0.5
Transfers (€)	0	5
Caregivers Training (€)	3	4.5
Total (€)	262	93

abandonment and stress (19, 20). In this way, caregivers act with a more consistent role in monitoring the outcomes of their relatives (21).

Our data confirm the potential of telehealth for the chronic management of TBI patients. As already demonstrated for other remote delivery systems proposed for elderly (8), PD or AD populations (11, 22), the feeling of being followed and cared at home plays a key role also in the clinical progression of severe TBI patients. Considering the recent statement of WFNR for telerehabilitation (http://wfnr.co.uk/), evidence on the effectiveness of telecounselling concluded that providing support to family members of people with TBI was beneficial (22) and that telecare is accepted by the vast majority of TBI patients and their careers (23). Studies on the effectiveness of the tele-based therapy in comparison with outcomes reached during usual LSH demonstrated significant improvements in global functioning, sleep quality, and depressive symptoms (24). Taking together all these findings we can conclude that telerehabilitation is as efficacious as usual in-person care for individuals with TBI (24, 25). However, considering the telemonitoring level, there is a paucity of data. For this reason, we believe that our preliminary study has the potential to increase the relevance of this kind of technology for the management of TBI patients. This is very important, considering that the main risk of TBI-related rehabilitation is that the recovery achieved in the hospital will be lost at home.

Limitations

Some limitations of this study need to be discussed. Firstly, our sample size was relatively small. However, it should bear in mind that to avoid spurious data coming from the well-known clinical heterogeneity characterizing TBI highly stringent inclusion criteria have been employed. Despite a perfect matching in demographical and clinical variables between groups at baseline, we recognized that a more exhaustive evaluation of medical complications during the follow-up period should be performed in further studies. Second, telemonitoring at home is generally more suitable for TBI patients with a stable clinical condition. Finally, the telerehabilitation technology is not always viewed by caregivers as a common practice, which can often require frequent consultations to SOU, causing a significant burden, especially in remote locations. Our system is considered feasible and accepted by all patients although evidence by satisfaction questionnaires was not provided since we are completing it.

CONCLUSIONS

Considering a mean follow-up period of approximately 4 years, we demonstrate that our telehealthcare service provides similar performance, as in-person usual care, to manage a complex neurological disorder such as TBI. As with other well-known telemonitoring programs based on a patient-centered approach to care, we also demonstrate that this kind of patient might be followed outside of the hospital in a cost-effective way, although deeper quantifications of direct/indirect costs are preferred. Further studies including different etiologies (i.e., vascular, anoxic) are needed to better define the limits of telehealth in DOC patients and to guide the policy decisions about the systematic use in health care (26). However, it is mandatory to translate the

feasibility and acceptability of this kind of telemedicine platform from neurological patients to other clinical domains. As recently stated by Maresca et al. (27), telemedicine services will contribute to a transformation of the entire healthcare sector and business models, mainly in the era of pandemics (i.e., COVID-19), where there is a need to avoid direct contact between clinicians and patients and to reduce the number of admissions at hospital.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Central Area Regione Calabria, Catanzaro, Italy. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Statistical analysis was done by SL, LM, and AC. The study design was done by LP, PT, and AC. Drafting the manuscript was done by AC, AM, and FC. Clinical data collection was made by FA, MGR, LR, and SS. Literature search, data interpretation, and revising the manuscript were done by FA, LP, PT, and AC. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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Virtual Reality for Motor and Cognitive Rehabilitation From Clinic to Home: A Pilot Feasibility and Efficacy Study for Persons With Chronic Stroke

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Aims: Continuity of care is an important issue in healthcare for persons after stroke. The present multi-center pilot study investigates the feasibility and efficiency of an innovative approach, the Human Empowerment Aging and Disability (HEAD), for digital-health motor and cognitive rehabilitation. The approach is explored within an in-clinic context (ClinicHEAD) and in continuity of care (HomeHEAD) for persons after chronic stroke.

Methods: Thirty-four outpatients with chronic stroke (mean age 55 years, SD 13.7) participated. The HEAD VR protocol was administered in two consecutive phases: Phase I in clinic (ClinicHEAD) consisting of 4 weeks of 12 supervised HEAD rehabilitation sessions (45-min), including motor, cognitive and dual task for all participants; Phase II at home (HomeHEAD) consisted of 60 sessions of the same VR activities, 5 times/week for 3 months. All participants in the ClinicHEAD were allocated (ratio 1:2) to continue with tele-monitored home rehabilitation (HH, $N = 11$) or to follow usual care (UC, $N = 23$). Blind evaluation was carried out at baseline, after ClinicHEAD, after 3 months of HomeHEAD and at 3 months Follow-up. Primary outcomes were functional mobility [2-min Walking Test (2MWT)] and cognition [Montreal Cognitive Assessment (MoCA)]. Feasibility and acceptance were assessed with adherence to treatment and the System Usability Satisfaction. Within group analyses were done with dependent samples t-tests, and between groups HomeHEAD comparisons were carried out on change scores with independent samples t-test ($p = 0.05$, two tailed).

Results: The HEAD protocol was feasible with good adherence both in the ClinicHEAD phase (92%) and HomeHEAD (89%) phase, along with good perceived system satisfaction. ClinicHEAD resulted in a significant increase in functional mobility (2MWT, $p = 0.02$) and cognition (MoCA, $p = 0.003$) and most secondary outcome variables. At 3 months follow up of HomeHEAD the HH_group showed a further significantly greater maintenance of functional mobility with respect to UC_group ($p = 0.04$).

Conclusion: The HEAD VR protocol was feasible in clinical and at home tele-rehabilitation for persons in the chronic phase after stroke. In clinic the approach was effective in augmenting motor and cognitive abilities and at home it was effective in longterm maintenance of functional mobility, indicating its usefulness in continuity of care.

Clinical Trial Registration: ClinicalTrials.gov, NCT03025126.

Keywords: stroke, hemiplegia after stroke, virtual reality, rehabilitation, continuity of care, mobility, cognition

INTRODUCTION

Neurological disorders, including post-stroke sequelae, are among the most common causes of longterm disability in the general population. Persons with hemiplegia after stroke are faced with multifactorial motor and cognitive disabilities making longterm neurorehabilitation crucial to prevent disease aggravations and enhance their activity levels and quality of life (QoL) (1, 2). Most moderate to serious stroke sequelae require periodic sessions of rehabilitation, or even hospitalization, making maintenance of results an essential aspect (2). Nonetheless, not all persons in the more chronic phase post-stroke can have access to longterm continuous rehabilitation, leading to non-optimal recovery and reduced functionality that further impacts upon participation in life situations.

The integration of Digital Health (DH) approaches, including innovative exercises performed in a virtual reality environment within a home rehabilitation program, are an attractive solution to continuity of care and can constitute a functional low-cost resource for monitoring and applying rehabilitation in new motivating ways (3). Virtual reality training has been implemented for balance training, for improving arm function and for cognitive training in persons with stroke (4–7).

Systematic reviews have demonstrated that rehabilitation incorporated in VR technology is feasible and sometimes even more effective than standard rehabilitation for improving motor and cognitive symptoms after stroke and that they can result in potentially better community integration (8–11). However, motivation and adherence to home rehabilitation protocols remain a concern making the setup of interesting DH approaches essential for the success of the approach (12–15). The inclusion of the gaming concept in rehabilitation has been demonstrated to make the clinical program more motivating and immersive, an important concept in continuation of rehabilitation care (16–19). Also, short video clips have historically been used to elicit emotion and motivate people with interesting results, indicating that their dynamic nature may provide a model more representative of reality (20, 21). Video clips that are meaningful to the person and incorporated in a rehabilitation gaming concept may be particularly motivating and useful for addressing the various motor and cognitive stroke sequelae that persons face post-stroke and during lifetime degenerative neurological disorders.

The Human Empowerment Aging and Disability program (HEAD), a virtual reality Digital Health neurorehabilitation to maintain and improve motor and cognitive function in persons with neurological disorders, was developed combining these two motivating approaches (22). The HEAD approach is thus based on the use of low-cost devices and multimedia content, including short motivating video clips of Radiotelevisone Italiana (RAI) programs within the context of VR serious gaming neurorehabilitation. The specific purpose of the present pilot study was to provide the initial evidence of the longterm effect of this innovative way of applying motor and cognitive rehabilitation administered first in a supervised way and then individually at home. The HEAD VR neurorehabilitation was applied in a multicenter study, the first 4 weeks under supervision in the clinic as ambulatory services (ClinicHEAD) and immediately after at home for 3 months (HomeHEAD). Participants in the study were persons with Parkinson's disorders (PD), Multiple sclerosis (MS) and persons in the chronic phase post-stroke. With this study setup the end users, therapists and patients/clients, learned how to use the system and problemsolve so that once in the home they were already familiar with the HEAD system. Feasibility aspects of the intervention for persons with PD, MS and post-stroke have already been published in Isernia et al. (22) and were found to be good, with high adherence and good perceived functioning in routine and participation in daily life, and a generally satisfying feedback regarding the acceptance of the HEAD technology. Further, recently published (23) results for persons with PD using the intervention were promising, in that the HEAD program resulted in improved motor and cognitive abilities after the ClinicHEAD and in preserved motor and non-motor function at follow up.

The present study focuses on outpatients with chronic stroke sequelae that participated in the HEAD approach. The improvement in various motor and cognitive functions, during a HEAD telerehabilitation carried out in the clinic and supervised by therapists and psychologists, will be verified for all participants with stroke. Consequently, difference in outcomes between those that continue with the HEAD rehabilitation care at home and those that follow usual care will be explored. Both at the end of the HomeHEAD rehabilitation period at 3 months after ClinicHEAD, and at follow up 6 months after ClinicHEAD.

The main hypothesis is that following a supervised outpatient HEAD telerehabilitation people with stroke that continue with the HEAD telerehabilitation approach at home for 3 months will maintain the effects better at the end of the follow up than those that proceed with usual care.

METHODS

Participants

The study was carried out as a multicenter study and included three different neurological disorders, however, in the present study only data on participants that were outpatients post-stroke

will be reported upon. Forty five persons, outpatients post-stroke, were consecutively recruited from 3 Italian clinical Centers: the Rehabilitation Center Villa Beretta of Lecco, the IRCCS Don Carlo Gnocchi Foundation of Milan, and District Clinic San Camillo of Turin. The study period lasted from March 2016 to December 2017.

The study protocol was approved by the local Ethical Committees of the three centers involved (Comitato Etico IRCCS Fondazione Don Gnocchi, Comitato Etico of the inter-company of Lecco, Como and Sondrio, Comitato Etico of the inter-company "Città della Salute e della Scienza" of Turin) and all subjects provided written and informed consent prior to participation in the study.

Inclusion criteria for the persons post-stroke was the following: age range of 18–80 and stroke in the chronic phase, at least 6 months after the acute event. Exclusion criteria included: (a) Mini Mental State Examination (MMSE) (24) score < 20; (b) the presence of disabling pain; (c) upper limb limited passive range of motion; (d) epilepsy; (e) severe deficit of visual acuity and auditory perception; (f) presence of severe deficit in communication and severe dysmetry.

The data analyzed and presented here is from a subgroup of the study participants that met the criteria of 80% adhesion to the study protocol and that could stand, even with support, for 30 s. The first criteria were used to respect the minimum rate of adherence needed to appraise the quality of the clinical trial (25) and the second because the primary motor outcome was the 2-minute walking test. This resulted in two persons being excluded from the analysis.

Study Design

The study was carried out in two steps: ClinicHEAD (Phase I) and HomeHEAD (Phase II). The ClinicHEAD consisted of a pre-post study to test the intervention delivery characteristics (safety, feasibility and acceptability, and appropriateness of measurements) and was carried out in the clinic [see Isernia et al. (22) for more detailed information]. Persons with stroke sequelae were consecutively recruited from persons that were requesting outpatient rehabilitative services from the respective centers. After enrollment and baseline assessment, they were all assigned into the ClinicHEAD program (Phase I) and received 12 sessions of VR training over a period of 4 weeks in-clinic outpatient services. During the month of in-clinic treatment the HEAD sessions (45 min three times per week) the participants were supervised by health professionals. Activities, repetitions and level of difficulty were tailored to each participant's abilities and constantly updated. Participants were encouraged to access the HEAD platform independently in order to develop problem solving techniques. The second part of the study was carried out as telerehabilitation in the home of the participants (HomeHEAD, Phase II) and consisted in a single-blind (observer), interventional, two-treatment arms (HomeHEAD vs. Usual-Care) controlled clinical trial. At the end of the ClinicHEAD the participants were consecutively assigned into either a HomeHEAD group [12 weeks of HEAD telerehabilitation (HH) at home] or a usual care group [12 weeks of Treatment as Usual (Usual Care, UC) at home] by a person outside of the study with a ratio of 1:2. This ratio was based on the pilot nature of the study and a limited number of available HomeHEAD technological kits for the time period of the study. This Phase II of the study served for an initial verification of efficacy of the approach compared to usual care in maintenance of in-clinic results and to evaluate the occurrence of adverse events.

Further details of the study protocol are given elsewhere [see Isernia et al. (22)].

Outcome Measures

Outcome measures were collected by researchers blinded to group allocation (observer-blind). Since participants could not be blinded to their treatment allocation, they were instructed not to discuss the nature of their intervention with the health professionals doing the assessments. Primary and secondary outcome measures were obtained: (a) at baseline (T0) before starting the 12 ClinicHEAD sessions; (b) at the end of the ClinicHEAD (T1) before starting the in-home HEAD sessions or the Usual care; (c) at post-HomeHEAD or Usual care, 3 months after (T2); (d) at follow up 7 months after baseline (T3).

The study timeline is illustrated in **Figure 1**.

This was a feasibility and pilot interventional trial used to identify the appropriateness of the outcome measures, and to generate effect sizes for a Phase III trial. The data analyzed here is of 34 persons that received the VR treatment during ClinicHEAD and HomeHEAD, and met the adhesion and standing criteria.

Intervention ClinicHEAD and HomeHEAD

The ClinicHEAD training was supervised by physical therapists and psychologists. The training was carried out with Kinect (Microsoft, WA, USA) and Leap Motion (Leap Motion Inc., CA, USA) in a room with an area of 20 m^2, three times a week for 4 weeks. The image was projected on a television screen with the participants placed in front with ample space to carry out the exercises. Instrumentation is described more in detail in Isernia et al. (22).

Motor, cognitive and occupational exercises were integrated in a paradigm of VR activities. Activities were coarsely divided into those that were more of type motor activities, cognitive activities or occupational activities. Motor activities included unilateral and bilateral arm movements, equilibrium exercises involving trunk movements, unilateral stance, reduced base of support and in place gait activities and leg movements. Cognitive activities requiring attention, memory, executive function and so on required hand movements for responses and also occupational activities, such as shaving, putting on make-up, doing a puzzle etc.

Each activity started with a short movie that was then interrupted periodically with motivating breaks that called for rehabilitative activities. Specifically, in the motor activities the movie was stopped in different moments of the movie clip. At each movie break a serious game, implying a rehabilitation activity, took place. The number of intervals were from 2 to 7 for each movie clip and were related to the difficulty level of the planned activities. Moreover, within the single movie break, the virtual activity requested a variable number of repetitions for the

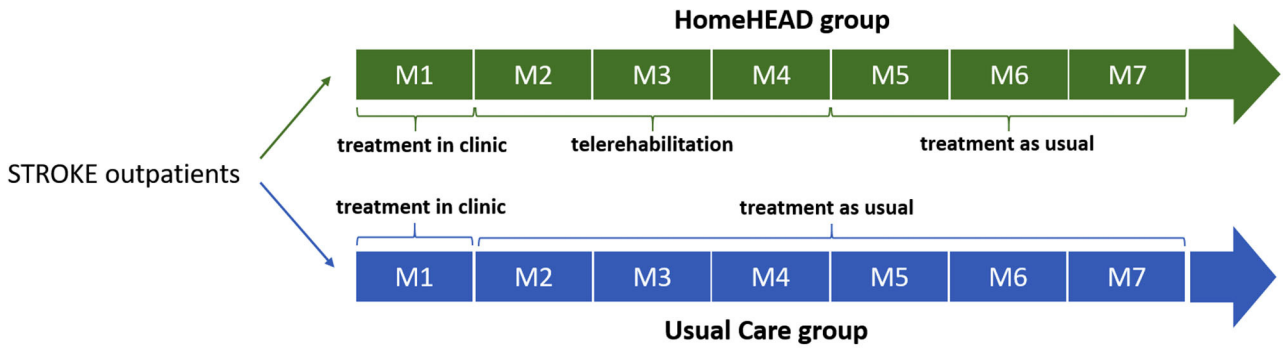

FIGURE 1 | Timeline of the HEAD trial in months.

specific neuromotor exercise set according to the intensity level of the rehabilitative activities programmed. During cognitive activities attention had to be payed to the content of the movie, requiring, for example, information to be memorized. The movie clips came from the historical collection of RAI documentaries and movies, and the movie clips shown were tailored to the participant's particular interests.

HomeHEAD Phase II

The HomeHEAD part followed the same principles of the ClinicHEAD but was carried out in the home of the participant without supervision. Training was programmed to be carried out five times per week for ∼45 min, and once per week the trained physical therapists and psychologists modified the program for the following week according to participants abilities. The HomeHEAD differed from the ClinicHEAD in that all motor and cognitive activities were carried out in a sitting position. The participants were invited to call the health personnel in case of difficulties with the setup or questions regarding the carrying out of exercises.

The UC participants were asked to not participate in physical activities different from those that they would usually do during the protocol duration.

Both the active group participants and the usual care participants were invited to follow health recommendations of their physician or neurologist for their clinical conditions.

Assessment Design and Outcome Measures

The assessment protocol consisted in multi-domains evaluation of feasibility, physical activity, motor and cognitive abilities, and QoL.

Feasibility of the intervention was assessed by participant adherence and perceived ease of use of the HEAD system. For perceived ease of use The System Usability Scale (SUS) (26) was administered at T1 (to all particpants) and T2 (only to HomeHEAD users). The scale consists of a 10-item scale with a score of 100 representing a perfect facility of use. A cut-off score indicating a satisfying level of usability is 68. Adherence was assessed as the percentage of planned sessions actually performed. Mean duration of motor and non-motor activities performed per session are also reported. Evaluation of motor and cognitive functions was carried out at T0, T1, T2, and T3 and was comprised of the following motor abilities and neuropsychological tests.

Two Minute Walk Test (2MWT) (27) and 10 Meter Walk Test (10MWT) (28) for evaluation of gait resistance and gait speed; Berg Balance Scale (BBS) (29), a test for the assessment of patient's static balance, and Box and Blocks Test (BBT) (30) for evaluating participant's dexterity and arm function; Motricity Index (MI) (31), an index for assessing the strength of key muscle groups in upper and lower limbs post-stroke. The Montreal Cognitive Assessment (MoCA) (32), a sensitive tool for global cognitive level assessment; Rivermead Behavioral Memory Test-Third Edition (RBMT-3) (33), an ecological battery for assessment of memory abilities.

Primary outcomes were the 2MWT and the MoCA. All other variables were treated as secondary outcomes.

Data Analysis

Statistical analysis was performed using Statistica software. Descriptive statistics were employed to evaluate efficiency and effectiveness. Normal distribution of variables was checked through the Kolmogorov-Smirnov normality test.

Intention-to-treat-analyses were used for all outcomes. If an individual's evaluation was missing at any assessment point, the individual's outcome of the last evaluation done was carried forward.

Efficacy of the HEAD intervention in the ClinicHEAD Phase within the whole group was verified with *t*-tests. Specifically, paired sample *t*-tests were performed to compare T1 vs. T0 outcome measures in the whole sample, and T2 vs. T1 in the HomeHEAD group and the UC group. For group comparisons we computed the change at T2 and T3 relative to beginning of HomeHEAD (T1) through calculation of change scores (Δvalues) from T2-T1 to T3-T1, and after that we adopted independent sample *t*-tests comparing HomeHEAD and UC groups' change values at 3 months and 6 months follow up of HomeHEAD.

Effect size of within group differences were calculated for ClinicHEAD. Effect sizes were interpreted as trivial ($d < 0.2$), small ($0.2\ d < 0.5$), moderate ($0.5\ d < 0.8$), and large ($d > 0.8$) (34, 35).

Results were considered statistically significant when *p*-value was <0.05, tests were two-tailed.

Estimation of sample sizes for a future study with adequate power was carried out on 2MWT results from T0 and T3 evaluations.

RESULTS

Thirty-four participants meeting the adhesion and standing criteria finished the Phase I ClinicHEAD (mean age 59 years (SD 13.6). All 34 persons that finished ClinicHEAD finished also the 3-month Phase II assessment (HomeHEAD $N = 11$ and Usual care $N = 23$ (see **Table 1**). Five persons in the UC_group were not available for follow up assessments at 6 month after ClinicHEAD due to difficulties in arriving to the Institutes for evaluation. Their data was treated as intention-to-treat for all analyses.

No study related adverse events were reported in the HH_group.

There were no statistically significant differences between the HH_group and UC group regarding age and onset while educational level resulted different. See **Table 1** for demographics and characteristics of the whole sample and the two subgroups.

TABLE 1 | Demographics and baseline characteristics of the ClinicHEAD and the HomeHEAD groups (UC and HH).

	ClinicHEAD	UC	HH	UC vs. HH
				P
N	34	23	11	
	Mean (SD)	Mean (SD)	Mean (SD)	
Age (Years)	59.00 (12.68)	60.19 (9.63)	56.72 (17.4)	0.365
Education [Mean (SD)]	13.56 (3.49)	12.71(3.16)	15.18 (3.65)	**0.028**
Sex (M/F)	18/14	13/8	5/6	0.465
Affected arm right/left	14/18	8/13	6/5	0.465
Motor functioning				
2MWT (Meters)	75.48 (45.83)	76.06 (52.8)	74.27 (35.26)	0.917
BBS	40.15 (15.58)	39.39 (16.14)	41.73 (14.95)	0.689
10MT (seconds)	15.67 (12.52)	17.38 (14.52)	12.09 (5.7)	0.255
MI_A	61.60 (26.35)	58.06 (26.35)	69 (25.34)	0.264
MI_NA	99.88 (0.68)	99.83 (0.83)	100.0 (0)	0.498
BBT—affected	15.4 (19.45)	11.87 (16.39)	21.82 (23.08)	0.157
BBT—non-affected	47.81 (12.31)	45.35 (8.57)	53.36 (16.17)	0.066
Cognitive functioning				
MoCA	22.56 (4.66)	21.91 (4.16)	23 (5.8)	0.536
RBMT-GMI	80.9 (17.42)	79.91 (17.46)	80.64 (17.7)	0.911

p-values < 0.05 are reported in bold; UC, usual care; HH, HomeHEAD; t2MWT, 2 m Walking Test; BBS, Berg Balance Scale; 10MT, 10 m Walking test; MI_A, Motricity Index Affected side; MI_NA, Motricity Index Not-Affected side; BBT, Box and Block Test; MoCA, Montreal Cognitive Assessment; RBMT-GMI, Rivermead Behavioral Memory Test-Third Edition—Global Memory Index; M, Mean; SD, Standard Deviation.

Feasibility

Adherence to the supervised ClinicHEAD was 92% of planned rehabilitation sessions while to the HomeHEAD it was 89%.

Out of 60 sessions maximum programmed for the HomeHEAD, an average of 55 (SD13.7) sessions were carried out. Mean daily time spent in VR activity was 35.3 min (SD 6.25), of which 18.6 (4.6) min were spent in motor activities and 10.7 min (3.7) and 6.3 min (3.4) were spent, respectively, in more cognitive and occupational activities. Over time of using the system there was an increase in perceived satisfaction with the system as measured by the SUS, after the intervention period the median total score of the 11 participants that continued to use the system at home (HomeHEAD, HH_group) was 77.5/100 (IQR 67.5–82.5) with learnability and usability subscores of 3.0 (IQR 2.5–4) and 3.0 (IQR 2.6–3.5) respectively. For more detailed information on system satisfaction for all neurological patients see Isernia et al. (22).

Efficiency

Changes in Outcome Measures After ClinicHEAD (T1-T0, $N = 34$)

Following the supervised ClinicHEAD sessions executed by the whole group, there were statistically significant improvements in both the primary motor outcome (2MWT: $t = 2.684$; $df = 33$; $p = 0.011$; Cohen's $d = 0.894$) and in the primary cognitive outcome (MoCA: $t = 3.644$; $df = 33$; $p = 0.001$; Cohen's $d = 1.253$). See **Table 2** for outcome values of ClinicHEAD.

TABLE 2 | Efficiency of the ClinicHEAD approach (T1-T0).

	T0 $N = 34$	T1 $N = 34$		
	Mean (SD)	Mean (SD)	*P*	Cohen's *D*
Primary outcome				
2MWT	75.48 (45.83)	82.95 (47.68)	**0.011**	0.894
MoCA	22.26 (4.69)	23.94 (4.2)	**0.001**	1.253
Secondary outcome				
BBS	40.15 (15.58)	41.78 (15.46)	**0.010**	1.067
10MWT	15.67 (12.52)	14.46 (12.17)	**0.005**	1.071
MI_A	61.60 (26.35)	64.65 (25.19)	**0.044**	0.595
MI_NA	99.88 (0.68)	100 (0)	0.324	0.349
BBT—affected	15.09 (19.05)	15.85 (20.30)	0.265	0.298
BBT—non-affected	47.81 (12.31)	49.21 (13.31)	**0.033**	0.639
RBMT-GMI	80.9 (17.42)	84.72 (19.2)	**0.032**	0.817

p-values < 0.05 are reported in bold. UC, usual care; HH, HomeHEAD; 2MWT, 2-m Walk Test; MoCA, Montreal Cognitive Assessment; BBS, Berg Balance Scale; 10MWT, 10 m walking test; MI_A, Motricity Index Affected side; MI_NA, Motricity Index Not-Affected side; BBT, Box and Block Test; RBMT-GMI, Rivermead Behavioral Memory Test-Third Edition—Global Memory Index; SD, Standard Deviation.

TABLE 3 | Means and SD of the HomeHEAD outcomes (T1, T2, and T3).

	T1		T2		T3	
	HH Mean (SD)	UC Mean (SD)	HH Mean (SD)	UC Mean (SD)	HH Mean (SD)	UC Mean (SD)
Primary outcome						
2MWT	84.36 (33.57)	82.28 (53.82)	92.45 (40.4)	80.69 (53.19)	90.63 (44.1)	76.35* (47.85)
MoCA	23.45 (4.34)	24.17 (4.21)	24.36 (4.24)	23.13 (4.21)	23.27 (5.92)	23.55 (4.22)
Secondary outcome						
BBS	43.37 (15.07)	41.65 (15.47)	42.27 (15.84)	40.43 (15.87)	43.45 (14.55)	39.26 (16.78)
10MWT	10.3 (6.23)	16.45 (13.85)	10.41 (7.44)	17.74 (15.2)	10.82 (7.03)	18.24 (15.38)
MI_A	72.04 (18.23)	61.11 (27.57)	70.63 (22.45)	63.12 (27.57)	76.27 (23.52)	61.74 (27.41)
MI_NA	100.0 (0)	100.0 (0)	99.64 (1.21)	99.83 (0.83)	100.0 (0)	100.0 (0)
BBT-affected	22.18 (23.62)	12.83 (18.31)	22.9 (24.26)	13.65 (20.14)	24.27 (25.36)	13.78 (20.12)
BBT-non affected	54.18 (16.77)	47.30§ (10.46)	53.9 (18.16)	48.56 (9.67)	57.45 (18.58)	49.83 (10.26)
RBMT-GMI	88.27 (18.75)	82.56 (18.76)	91.64 (18.62)	86.13 (20.73)	93.27** (19.17)	88.6 (20.18)

*$p < 0.05$, significant worsening T1-T3; **$p < 0.05$, significant improvement T1-T3; §$p < 0.05$, significant differences between groups at T1; UC, usual care; 2MWT, 2-min Walk Test; MoCA, Montreal Cognitive Assessment; BBS, Berg Balance Scale; BBT, Box and Block Test; 10MWT, 10 m walking test; MI_A, Motricity Index Affected side; MI_NA, Motricity Index Not-Affected side; RBMT-GMI, Rivermead Behavioral Memory Test-Third Edition—Global Memory Index; SD, Standard Deviation.*

Regarding secondary motor outcomes, there were statistically significant improvements in balance (BBS: $t = 2.722$; $df = 33$; $p = 0.010$; Cohen's $d = 1.067$); in gait velocity (10MWT: $t = -2.962$; $df = 33$; $p = 0.006$; Cohen's $d = 1.071$); memory (RBMT: $t = -2.253$; $df = 33$; $p = 0.031$; Cohen's $d = 0.817$); motor function of the affected side (MI: $t = 2.094$; $df = 33$; $p = 0.043$; Cohen's d = to do) and in ability of the non-affected arm (BBT: $t = 2.227$; $df = 33$; $p = 0032$; Cohen's $d = 0.639$).

HomeHEAD (T1-T2-T3)

At discharge the ClinicHEAD group was randomized 1:2 into the groups HH ($N = 11$) and UC ($N = 21$) with baseline characteristics of the two treatment groups being similar in terms of age and onset of stroke ($P > 0.05$) while in terms of educational level they differed by 0.85 years of education ($p = 0.03$). Regarding differences at baseline of the HomeHEAD phase all group specific outcome values at all time points are given in **Table 3**. The two groups were balanced in motor, cognitive and qualitative measures ($P > 0.05$) at T1 while there was a statistically significant difference on the Box and Block Test of the non-affected arm ($p = 0.011$).

Motor and Cognitive Outcomes

Within Group Differences (T2-T1) and Comparison Between HH and UC Group at End of HomeHEAD Intervention (ΔT2-T1). See **Table 3** for outcomes for T1 to T2 and T3, and **Table 4** for change scores and statistical significance.

Regarding the efficacy of the HomeHEAD, after 3 months of the VR approach the HH_group maintained the benefit from ClinicHEAD with no significant improvement nor decline in any outcome variable (T2-T1; $p > 050$). Similarly, in the UC_group there was maintenance of the positive effects of the ClinicHEAD with no significant change in any outcome variable (T2-T1; $p \geq 0.05$).

Between groups analysis through change scores revealed no significant difference in change scores of primary or secondary outcomes between the HH_group and UC_group from the beginning of HomeHEAD (T1) to end of the 3 months of HomeHEAD (T2) (ΔT2-T1; $p > 0.05$).

Within Group Differences (T3-T1) and Comparison Between HH and UC Group at HomeHEAD Follow Up (ΔT3-T1)

See **Table 2** for outcomes for T1 to T2 and T3, and **Table 3** for change scores and statistical significance. Regarding the maintenance of the HomeHEAD effect, at the 3 months follow up after HomeHEAD the HH_group had a significant improvement in memory (RBMT: T3-T1 $t = 3.741$; $df = 10$; $p = 0.001$) with respect to T1 and overall maintained the benefit from ClinicHEAD with no significant improvement nor decline in any other outcome variable. At the 3 months follow up after HomeHEAD the UC_group had a significant decline in functional mobility (2MWT: *T3-T1;* $t = -2.446$; $df = 22$; $p = 0.02$) with respect to T1 while overall there was maintenance of the positive effects of the ClinicHEAD with no significant change in any other outcome variable ($p \geq 0.05$).

Between groups analysis through change scores revealed significant difference in change scores of primary outcome functional mobility between the HH_group and UC_group from the beginning of HomeHEAD (T1) to end of follow up period (T3) (2MWT: ΔT3-T1: $t = -2.242$; $df = 32$; $p = 0.032$) with the HH_group showing improvement and the UC group detoriation of the parameter; and similarly, in secondary outcome motricity of the affected site (MI: ΔT3-T1: $t = -2.21716$; $df = 32$; $p = 0.034$).

Sample size estimation for a future study, assuming a value for alpha of 0.05 and a desired power of 0.8, with mean increases on the 2MWT of 0.28 meters for the UC_group and 13.36 meters for the HH_group (T3-T0) and pooled standard deviation, revealed the need for at least 38 persons with chronic stroke per group.

TABLE 4 | Comparison between UC and HH groups on neuropsychological and motor measures after 3-months of HomeHEAD/UC (ΔT2-T1) and after 6-months from ClinicHEAD (ΔT3-T1).

	ΔT2-T1			ΔT3-T1		
	HH	UC		HH	UC	
	Mean (SD)	Mean (SD)	*p*	Mean (SD)	Mean (SD)	*P*
Primary outcome						
2MWT	8.09 (20.19)	−1.59 (9.73)	0.066	6.27 (20.19)	−5.93 (11.63)	**0.032**
MoCA	−1.09 (2.34)	0.48 (2.1)	0.059	−0.18 (2.68)	−0.61 (2.82)	0.678
Secondary outcome						
BBS	−1.09 (5.17)	−1.22 (5.56)	0.95	0.09 (9.33)	−2.39 (8.44)	0.443
10MWT	0.10 (1.88)	1.29 (4.69)	0.899	0.51 (2.89)	1.79 (4.94)	0.434
MI_A	−1.41 (10.0)	2.01 (11.9)	0.41	5.64 (7.51)	−1.38 (9.09)	**0.034**
MI_NA	−0.36 (1.21)	−0.17 (0.83)	0.59	0.36 (1.21)	0.17 (0.83)	0.596
BBT_A	0.73 (1.74)	0.82 (2.60)	0.91	2.09 (3.7)	0.95 (2.8)	0.324
BBT_NA	−0.27 (5.68)	1.26 (5.78)	0.91	3.27 (6.02)	2.52 (5.39)	0.380
RBMT-GMI	3.36 (10.93)	3.56 (14.85)	0.968	5.00 (3.74)	6.04 (16.11)	0.834

p-values < 0.05 are reported in bold. HH, HomeHead; UC, usual care; HH, HomeHEAD; 2MWT, 2-min Walk Test; MoCA, Montreal Cognitive Assessment; BBS, Berg Balance Scale; 10MWT, 10 m Walking Test; MI_A, Motricity Index Affected side; MI_NA, Motricity Index Not-Affected side; BBT, Box and Block Test; RBMT-GMI, Rivermead Behavioral Memory Test-Third Edition—Global Memory Index; SD, Standard Deviation.

DISCUSSION

The present multi-center pilot study investigated the feasibility and preliminary efficacy of an innovative VR approach including short motivating video clips from RAI programs within the context of neurorehabilitation in clinic (ClinicHEAD) and in continuity of care (HomeHEAD). The approach was feasible and the technical complexity was acceptable to the participants that were in the chronic phase after stroke. Following the first supervised ClinicHEAD phase executed by all participants there was an overall improvement in most motor and cognitive domains. At the end of the 3 months HomeHEAD phase there was good compliance to the HomeHEAD protocol and both groups preserved their ClinicHEAD results. However, there was a better preservation of mobility in the HH_group at the end of the 3 months HomeHEAD follow up period.

Participants were on the average 15 months post-stroke and were quite heterogeneous in their functional and cognitive abilities. Adherence was good in both the ClinicHEAD and the HomeHEAD phase with satisfying feedback regarding system usability and learnability. The adherence of our stroke participants was in line with that reported in the literature (36). Importantly, there were no adverse events registered in either rehabilitation phase and all points to the HEAD VR approach being a safe, doable and motivating approach to neurorehabilitation in continuity of care. The inclusion of the video clips and the weekly adjustment of exercises according to abilities in the HEAD approach may have positively influenced the adherence.

ClinicHEAD (T1-T0)

Following the 12 sessions of ClinicHEAD we saw improvements in most aspects of motor and cognitive abilities. Although there was great heterogeneity in walking abilities of the participants, after the first 12 supervised sessions there was an overall improvement in gait velocity and gait resistance of about 20%, indicating that the ClinicHEAD approach was beneficial for walking activities. Even if there was no direct overground walking or training the HEAD protocol included dynamic activities in standing, such as, walking on the spot and knee raises relative to virtual activities of walking and stair climbing, that appear to have been beneficial for overground walking abilities of the participants. The improvement seen in real life mobility after a month of the HEAD VR protocol is promising and is in line with the results of several literature review on the effect of VR protocols on gait and balance in persons post-stroke (4, 6, 9, 12). The results also concord with recent literature reporting on trials using a VR approach to rehabilitation of gait and balance (37, 38).

Although cognitive impairment is common in the chronic phase after stroke and there is an evident connection between cognitive and motor deficits the impact of combining motor and cognitive aspects in VR approaches has been poorly investigated (3, 39). Following ClinicHEAD we saw small but significant positive changes (<10%), both in global cognitive functions and memory. These cognitive benefits are in line with findings from a random controlled VR trial carried out by Faria et al. (40) and a couple of reviews looking at both motor and cognitive outcomes after VR approaches (41, 42). Both reviews found a small to medium effect favoring a VR approach compared to conventional therapy with bigger effects on motor outcomes similar to that seen in our study. The above gives support to combining motor and cognitive training in VR approaches.

The HEAD approach did, however, not impact on hand function. This may be because there was great heterogeneity in affected arm abilities of our study participants and it should be noted that the participants that were more severely affected often used the not affected limb during the VR rehabilitation resulting in little or no training of the affected arm and hand. Further, even when the affected arm was used for the VR activities, the amount

of time spent in arm activities was only about 50%, the rest of the activities were focused on trunk and lower limb activities. This may have influenced the interventions efficacy on arm function since intensity and repetition are especially important in arm rehabilitation for persons with chronic stroke (43). Our results add to controversial results of other studies on VR and game applications that have been used to rehabilitate arm function in persons with chronic stroke (9, 11).

The present study was a pilot study and the ClinicHEAD was carried out on all participants with no control group, however, the participants were all in the chronic phase where it is known that there is little recovery if there is no intervention. The ClinicHEAD thus served as a training and getting to know the system phase, all participants had the same training and so had the same base for the HomeHEAD phase that instead was experimental and had the purpose of inquiring upon the effect of bringing a known system home for further training.

HomeHEAD, Usual Care, and Maintenance at Follow Up (T2-T1, T3-T1)

The main results of our study are that HomeHEAD impacted on longterm maintenance of functional mobility. Six months after ClinicHEAD, at 3 months follow up of HomeHEAD, the HH_group had increased the distance they could walk in 2 min while the UC_group had lost some mobility, resulting in a significant difference between the two groups in preserving mobility results over the 6 months. This is an important result since mobility and gait speed are important aspects of health and have been demonstrated to be predictive of life participation and need for hospital recovery (44, 45). Thus, potentially, bringing the HEAD system home preserved mobility functions in our HH_group and delayed the need for further care. Moreover, there was an improvement in memory at 6 months from ClinicHEAD only in the HH_group, indicating further longterm benefit on memory from bringing the HEAD system home.

Regarding the effect of bringing the HEAD system home for daily weekday training, there was no further increase in any motor or cognitive outcome immediately after 3 months of HomeHEAD. Importantly, there were no differences in maintenance of ClinicHEAD benefits between the participants doing HomeHEAD training and those that followed usual care. Both groups preserved the results achieved. One of the reasons for no further improvements in the HH group may be due to effects of any intervention being largest in the first couple of weeks of intervention, such as, that seen by Krakauer et al. (46). It may be an unrealistic goal to expect further significant improvement in motor and cognitive outcomes after 4 weeks of ClinicHEAD treatment.

In their review Aminov et al. (41) looked at follow up data from VR training and interestingly found no difference between effects immediately following training and follow up end point. The studies reviewed all had between 6 and 12 weeks follow up so our finding of preserving of initial VR training results at 3 months for the UC_group are in line with the review's findings. At 6 months without training there was, however, a detoriation of mobility in the UC_group compared to the HH_group that was only at 3 months follow up from end of HomeHEAD. Regarding the longer-term efficiency of the HomeHEAD approach, this would have to be studied in future studies with longer than 3 months follow up.

General Discussion and Limitations

While most people with chronic neurological disorders experiment the major part of functional recovery while in clinic, many could continue to improve, or at least, preserve abilities, over longer time periods. Patient engagement in the paradigm of rehabilitation in continuity of care is an important issue. With motivated engagement of the chronic patient they can become main actors responsible for their life and health care and can be accompanied by the health care system rather than being dependent on it (22). Telerehabilitation using VR systems is useful for manipulating and augmenting the interaction between the user and the environment, with the objective of impacting on neuromotor and cognitive recovery, ultimately leading to increased activity and daily life participation. The use of VR systems in rehabilitation is consequently an important option both during recovery and in continuity of care. In particular, they become essential for persons living in rural zones or persons that for some reason have limited access to rehabilitation care.

Our VR HEAD study is a multicenter study that was carried out by a multidisciplinary team. The training protocol was developed in collaboration between different health professionals and was aimed at improving many aspects of health of the individual, motor and non-motor, resulting in a complex intervention in line with that recommended by Langhorne (44). The HEAD training strategies allowed an interplay between therapeutic goals and individual abilities, with regular adaptation of difficulty so that it progressively demanded more of the person in training (47). At the end of the follow up period there was an important maintenance of mobility in the participants that brought the system home, an aspect of functioning that is partly indicative of independence in daily activities and mobility out of the home. This indicates the HEAD multidisciplinary approach to rehabilitation may be well-suited for continuity of care, it is ecologically valid and effective without interfering with the persons everyday living activities and can potentially progressively augment autonomy and ability of the person in training (22, 23, 48).

Importantly, the HEAD approach was viewed positively by most of the persons playing it with no distinction of age or sex and the majority of the persons using it during the in-clinic phase were convinced they would use it in the home setting if the opportunity arose. One of the major benefits of the HEAD VR system is in fact the possibility to continue rehabilitation under occasional supervision of health professionals (theoretically infinitely) for much longer than would otherwise be possible. With the VR serious games approach therapy can be incorporated into daily home and work activities thus reducing cost to society in terms of home assistance or absence from work. Further, the opportunity of longer rehabilitation time will allow bigger improvement and/or longer maintenance of function which is important for persons with neurological disorders that need to both consolidate the

results obtained during recovery in rehabilitation centers and continue improving their function in their daily habitat.

A strength of the study approach used in the present study is the fact that both groups carried out the same VR rehabilitation during the 4 weeks in clinic, while only after that they are split up into an experimental and a control group, thus the groups share a phase in rehabilitation period. Any change or better maintaining of these in clinic treatment effects can thus be attributed to the HomeHEAD intervention rather than being an effect of beginning a new rehabilitation activity as described by Dobkin and Carmichael (49).

Our pilot study, however, has several limitations, first of all for not being a random controlled trial with equal sample sizes. Generalization of results is also limited to persons with chronic stroke that adhere to the protocol and are able to stand at least 30 s. Another limit, shared with most other studies in the literature studying the effect of VR home rehabilitation, is that the sample participating was small so conclusions can only be indicative as to efficiency of the approach. However, the study has provided indications of feasibility and an estimation of the potential efficiency and effect sizes of a motor and non-motor telerehabilitation protocol (HEAD) for people with chronic stroke that will be useful in future larger Phase III trials.

Yet another limitation might be the use of a passive control group in the HomeHEAD phase, however, Aminov et al. in their systematic review (41), found no difference in effect sizes of virtual reality outcomes when compared to either active and passive control groups suggesting that the use of a passive control group may not have impacted on the outcome.

Conclusion

There was an increase in most evaluated motor and cognitive outcomes following 12 in-Clinic sessions of the HEAD VR approach indicating that with this global approach to rehabilitation it is possible to impact on many of the deficits that persons with chronic stroke have to live with. Importantly, use of the approach in continuity of care may have increased longterm maintenance of mobility, an important aspect of daily functioning. Over the lifetime of having a neurological disorder multidisciplinary rehabilitation is an integral part of improvement and maintaining of functionality and likely, virtual reality approaches will be part of future longterm neurorehabilitation solutions.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by IRCCS Don Gnocchi Foundation Ethical Committee, Intercompany of Lecco, Como, and Sondrio Ethical Committee, Intercompany of Citta della Salute e della Scienza of Turin Ethical Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

FB, MS, and FM conceived the study. CP, CC, CG, and TB recruited sample and did clinical evaluation. JJ, PG, GPa, and GPe collected data. JJ, SD, SI, and FB performed analysis and interpreted the results. JJ, SI, and FB wrote the first draft of the manuscript. All authors reviewed and approved the final manuscript.

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HEAD STUDY GROUP

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BRIEF RESEARCH REPORT
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The Time Burden of Specialty Clinic Visits in Persons With Neurologic Disease: A Case for Universal Telemedicine Coverage

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Objective: Those with chronic neurologic disorders are often burdened not only by the condition itself but also an increased need for subspecialty medical care. This may require long distance travel, while even small distances can be a hardship secondary to impaired mobility and transportation. We sought to examine the burden of time associated with clinical visits for those with chronic neurologic disorders and their family/caregivers. These topics are discussed as an argument to support universal coverage for telemedicine in this population.

Design: Cohort Study.

Setting: Specialty clinic at community hospital.

Participants: 208 unique patients with chronic neurologic disability at physical medicine and rehabilitation or neurourology clinic over a 3-month period.

Main Outcome Measures: Patient survey on commute distance, time, difficulties, and need for caregiver assistance to attend visits.

Results: Approximately 40% of patients were covered by Medicare. Many patients (42%) perceived it difficult to attend their clinic visit with transportation difficulties, commute time, and changes to their daily schedule being the most commonly cited reasons. Most patients (75%) lived within 25 miles of our clinics and experienced an average commute time of 79.4 min, though 10% required 3 h or more. Additional family/caregiver assistance was required for 76% of patients, which resulted in an inclusive average commute time of 138.2 min per patient.

Conclusion: Chronically neurologically-disabled patients and their caregivers may be burdened by the commute to outpatient appointments. To minimize this burden, increased emphasis on telemedicine coverage for those with chronic neurologic disability should be considered by all payors.

Keywords: telemedicine, burden, neurological disorders, disability, caregiver, commute time

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INTRODUCTION

With the advent of subspecialty care for persons with chronic neurologic disorders, there have been substantial efforts to improve both health outcomes and patient satisfaction (1–3). However, persons afflicted with chronic neurologic disorders often have dysfunction in more than one organ system requiring subspecialty care from multiple providers on an ongoing basis. In many instances, for those with chronic neurologic disability, care is not available in a multidisciplinary fashion and leads to multiple clinic visits on varying days (4). In addition, specialty physicians are not always available in a patient's local community, which can result in long distance travel to obtain appropriate care (5, 6). For many persons with chronic neurologic disability, the time spent attending repeated medical visits can disrupt their personal and professional lives, and results in a significant ongoing burden to them and their caregivers (7, 8).

In recent years, to address barriers to care, telemedicine has been introduced to provide convenient patient care (4, 8–13). As seen during the COVID-19 outbreak, telemedicine has expanded to include live synchronous audiovisual conference, store-and-forward videoconferencing, remote patient monitoring, and general education information (14). Compared to traditional in-person medical visits, telemedicine visits can be performed remotely, often from the convenience of a patient's home or place of employment (15–17). Overall, patient and clinician satisfaction with live telemedicine visits are reported to be high with comparable health related outcomes to in-person visits (8, 10, 18–20).

However, outside of temporary changes brought about by the COVID-19 pandemic, telemedicine is still not a universally patient-covered benefit and reimbursement for telemedicine, even if covered, is not always straightforward. For example, Medicare beneficiaries with neurologic disorders (including, individuals over 65 years old with Medicare coverage, individuals <65 years old receiving Social Security disability as a result of a debilitating neurologic condition, or individuals with amyotrophic lateral sclerosis), receive restrictive telemedicine coverage (21). Specifically, for telemedicine to be covered by Medicare, the beneficiary must physically be in a health care clinic or inpatient hospital setting, and also be in a rural location where access to a specialist may be unavailable (22). Currently, once coronoavirus-19 pandemic provisions expire, Medicare will not cover telemedicine visits with their specialists if the individuals are at home. As a result, those with chronic neurologic disease and their caregivers may continue to require substantial amounts of time to coordinate and travel to in-person visits with their physicians.

To date, the overall "time burden" that is shouldered by those with chronic neurologic disability to physically attend clinic visits in person has been incompletely evaluated. A greater understanding of the time burden and the patient experience may facilitate the promotion of telemedicine coverage. This study examined the time burden and difficulties of patients and their caregivers attending clinic visits in a specialty center.

METHODS

We conducted a survey-based quality improvement project at a community specialty outpatient clinic in Northern California from January 1, 2019 to March 1, 2019. The study was deemed a quality improvement project and was exempt from Institutional Review Board review. During the study period, all patients with chronic neurogenic disorders receiving outpatient clinical care from either the Department of Physical Medicine and Rehabilitation or Division of Urology were administered a twenty-question paper survey regarding distance traveled, transportation difficulties, and the time required for the patients and their caregiver to prepare and commute to their appointments (**Supplementary Material 1**). In cases where the patients themselves could not complete the form due to a limitation, assistance was rendered by the patient's caregiver or clinic staff. Patients <18 years old, those completing a questionnaire at a previous visit, or those unable to comprehend the English language-based questionnaire were excluded. No patient refused participation. The survey included questions regarding patient demographics, distance traveled, transportation difficulties and the time required for the patients and their caregiver to prepare and commute to their appointments.

Following study completion, all survey information was databased in Excel. The patients commute time was calculated by combining the patients' reported travel time to and from the clinic. A minority of patients ($n = 12$) included time for their trip to the clinic but not back home. For these patients, the reported time to clinic was simply doubled. In rare cases where distance and time estimates were not answered ($n = 14$), the estimated distance from the patient's home to clinic was computed using Google maps with departure set to noon on the weekday of the clinic visit (https://www.google.com/maps). In addition to patient commute and preparation time to clinic, the study also included the time a patient family member or caregiver spent coming to clinic, when applicable (max of one person since multiple caregivers were not discernable by our survey).

RESULTS

There were 208 independent completed questionnaires. The median age of the population was 49.0 years with a median of 4.0 years since the onset of neurologic disability. A greater proportion of the population was male (63.5%) and the most common neurologic diagnosis in the study population was spinal cord injury (SCI) (37.0%), followed by non-traumatic brain injury (20.2%), and traumatic brain injury (13.5%), with cerebral palsy, multiple sclerosis, and spina bifida making up the remainder. The insurance status of the study population was mixed. Most patients were covered by Medicare (38.0%) or Medicaid (California Medicaid) (34.6%), with the remaining 27.3% covered by private insurance, Workers' Compensation, or in rare cases no insurance coverage. The majority of patient visits were to physiatrists (88.9%) with a minority to a neuro-urologist (13.0%) (several as joint appointments) (**Table 1**).

TABLE 1 | Population demographics, injury characteristics, and transportation.

Sample characteristics	
Characteristic	**Median (IQR)**
Age (years)	49.0 (34.2–60.9)
Years since injury	4.0 (1.0–19.5)
Gender	***N* (%)**
Male	132 (63.5%)
Female	76 (36.5%)
Insurance	
Medicare	79 (38.0%)
Medicaid	72 (34.6%)
Private	38 (18.2%)
Workers' Comp	18 (8.6%)
No insurance	1 (0.5%)
Visit type*	
Physical Medicine & Rehabilitation	185 (88.9%)
Urology	27 (13.0%)
Neurologic disorder	
SCI/transverse myelitis	77 (37.0%)
Non-traumatic brain injury (stroke, tumor, other)	42 (20.2%)
Traumatic brain injury	28 (13.5%)
CP	13 (6.2%)
MS/neuromyelitis optica	5 (2.4%)
Spina bifida	5 (2.4%)
Other	20 (9.6%)
No response	18 (8.6%)
Caregiver/family present	
Yes	158 (76.0%)
No	50 (24.0%)
Transport method	
Personal car—driven by family/friend	105 (50.5%)
Personal car—patient driven	38 (18.3%)
Wheelchair van (scheduled)	32 (15.4%)
Car service (cab, rideshare)	11 (5.3%)
Public transit/bus	7 (3.4%)
Ambulance	2 (1.0%)
Other/unknown	13 (6.2%)
Transit payor	
Patient/family	131 (63.0%)
Insurance	34 (16.3%)
Other/unknown	43 (20.7%)
Wheelchair use	
Used for visit	105 (50.5%)
Not used for visit	89 (42.8%)
Unknown	14 (67.3%)

**Patients could see more than one provider on the same day.*
SCI, spinal cord injury; CP, cerebral palsy; MS, multiple sclerosis.

The mean distance from a patient's home to the clinic was 23.3 miles with roughly one fourth of the population commuting >25 miles (range 0.25–315 miles) (**Figure 1**). Patients commuted to the clinic in a variety of ways, most commonly in a personal car driven by family or friends (50.5%), followed by patient-driven car (18.3%), and hired wheelchair van (15.4%). Two patients were brought by non-emergent ambulance. Transit costs were largely reported to be paid by patients or family (63.0%), with 16.3% reported to be paid through insurance (**Table 1**). Of a subgroup of patients who reported travel costs ($n = 65$), a mean cost of $39.10 (range 0–$400) was reported.

The study population estimated that they required a mean of 79.4 min to commute to their clinic visit and back home, with 10% requiring more than 3 h of commute time (**Figure 2**). Patients were often accompanied to the clinic by either a family member (63.5%) or caregiver (12.5%). When accounting for the additional time spent by family or caregivers, the calculated time estimates increased to a mean total of 138.2 min commute time with 19% requiring over 3 h of commute time (**Figure 3**).

Roughly 40% of the study population noted difficulties coming to their clinic visit. Specific difficulties mentioned included transport itself or arranging transport (35.6%), time spent commuting to clinic (27.6%), their health condition (18.4%), parking (17.2%), changes to their daily schedule (16.1%), trouble transferring from their vehicle to a wheelchair (6.9%), and out of pocket cost (2.3%), with some patients mentioned more than one difficulty (**Table 2**). Of those reporting a need to make special arrangements for transportation to clinic, it was estimated that an average of 18 min was required, and the arrangements generally needed to be at least a week prior to their visit.

DISCUSSION

No matter our goals in life, a key component is the time to pursue them. In persons with neurologic disorders, simple activities of daily living often are more time-consuming and inconvenient to perform. An increased need for medical care only further increases the time burden to their daily life. We find that individuals with chronic neurologic disorders require substantial amounts of commute time to and from medical visits, with the average patient requiring 79.4 min, and about 10% spending more than 3 h per visit. In addition, family and caregivers are also affected, as more than 75% of patients had a family member/caregiver present at their appointment. Taken together, the time burden of clinic visits is more pronounced, with an average total commute time of 138.2 min with ∼20% requiring 3 or more hours. As we would surmise that visit times with a health care provider (whether in-person or via telemedicine) are 15 min based on clinical templates, a key difference between visit types would be the travel time.

The time burden that individuals with chronic neurologic disability and their family/caregivers face in receiving medical care can be influenced by geographic, physical, psychosocial, or transportation related barriers (5, 23–26). We found that 41.8% of patients reported difficulty in attending clinic visits.

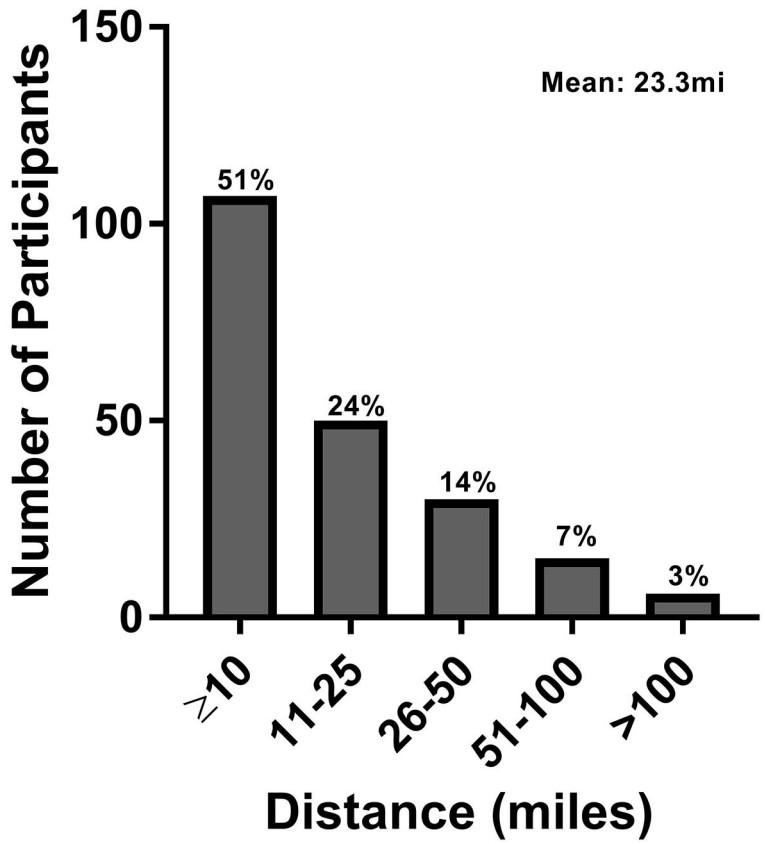

FIGURE 1 | Patient distance between home and clinic.

Transportation difficulties, commute time/preparation time, and changes to their daily schedule were the most commonly cited reasons (**Table 2**). These difficulties may disproportionately affect individuals with chronic neurological disabilities compared to abled-bodied individuals. As such, telemedicine visits may reduce these obstacles significantly (27) with prior studies demonstrating SCI patients endorsing telemedicine as easy to use, efficient and convenient with high patient perceived health satisfaction (8, 20).

To date, while many studies have shown increased patient satisfaction and comparable care outcomes with the use of telemedicine, few have focused on the convenience it offers specifically from a time perspective (8, 20, 28). Two studies of Veteran Affairs patients in Atlanta and Los Angeles with large catchment areas found an average per patient time savings of 3–4 h for those attending urology appointments (29, 30). Other studies have found a reduction in average round trip commute time of 39 min per patient for those attending vascular surgery clinics and 80 min for outpatient orthopedic surgery follow-ups (31, 32). Our findings of ∼79.4 min spent commuting to and from a clinic visit in a population with chronic neurologic disorders are comparable; however, when factoring in the need for family/caregiver assistance, these estimates increase substantially. The family/caregiver component should also be viewed as an additional stress on a patient's support system where caregivers are often required to miss work to attend appointments, and caregiver burnout is prevalent (33). Easing not only the time and financial constraints but also the psychological burden on patients and their caregivers should be considered.

While some insurers now cover telemedicine encounters between a physicians' office to a patients' home/workplace, coverage is far from universal. For instance, Medicaid in certain states has restrictive requirements pertaining to patient location and distance from their provider while Medicare has yet to cover telemedicine, except in limited circumstances. As 38% of our study population falls into Medicare coverage (mostly due to chronic neurologic disability) a substantial proportion of our patients are ineligible to receive remote care at home. Prior to the recent COVID-19 outbreak, which has temporarily lifted Medicare telemedicine restrictions, it has been speculated that Medicare was reticent to widely adopt telemedicine secondary to fears of overuse and increasing costs to the system. However, there is evidence that telemedicine may decrease costs in those with chronic neurologic disorders as illustrated by a study of amyotrophic lateral sclerosis patients who utilized less home health care and had a lower risk of disease progression when using telemedicine compared to

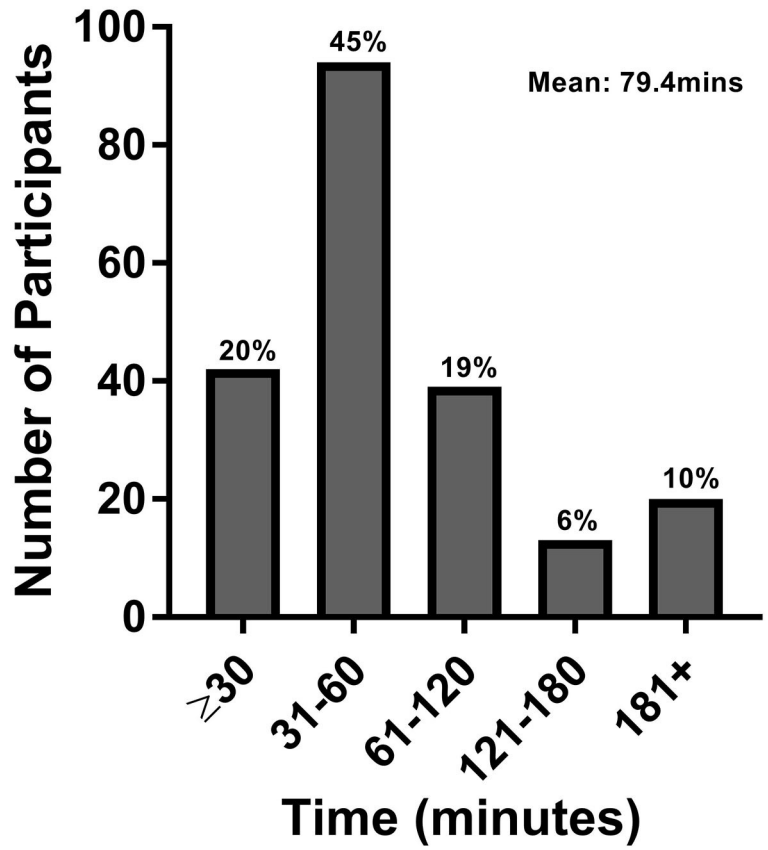

FIGURE 2 | Patient commute time. This figure represents the total roundtrip commute time in minutes for patients only.

those utilizing regular clinic care at a tertiary care center (19). In addition, when one further considers the need for specialized transportation required by some of our population (16% of our sample has their transportation reimbursed by insurance), additional savings could be realized as Medicare reimbursements to medical transport companies are ∼$500 for a 30-mile roundtrip in a basic life support ambulance in California's Bay Area. Further, telemedicine visits are reimbursed the same as in-office visits despite the capital outlay of electronic platforms a physician's office would need to cover. When one further considers that no-show rates of up to 17% have been documented in SCI patient visits to specialty centers, telemedicine may also improve physician efficiency and patient access, as fewer rescheduling of appointments would be required (34).

We have noted significant improvements in our ability to complete patient visits using telephone visits during the COVID-19 outbreak with a near 100% visit rate to date, and numerous patients wondering if telemedicine visits can be continued long-term. While it can be argued that telemedicine is unable to offer full physical exams, in our experience, following a patient's initial patient evaluation, most follow-up visits do not involve further physical examination. This was evidenced during the study period in the subgroup of urology patients undergoing follow-up visitation in whom 18/20 (90%) did not require physical examination; one patient needing a post-void residual check and the other a measurement of upper extremity motor function. This may argue that one can eliminate travel times and in-person visits for many patients with chronic neurologic disability, with the prospect of more worthwhile patient and caregiver experiences over their long-term care horizon.

Telemedicine is a logical extension of societal trends of digital communication with more than half of medical schools already incorporate telemedicine training into their clerkships (35). As of 2016, it is estimated that 89% of United States households have a computer or smartphone and 81% have a broadband internet subscription that will provide the basic technology to perform a telemedicine visit (36). This data may also suggest that there is a reduced burden for individuals to adopt this technology.

There are different ways to calculate the cost savings of telemedicine usage. One method is to assess the cost of time gained, from not commuting to clinic. For instance, if every patient paid for (or was given) the preferred mode of telecommunication at our institution (an Apple iPad, current cost is $329). Using average commute times, the cost to families to avoid travel and preparation time would be

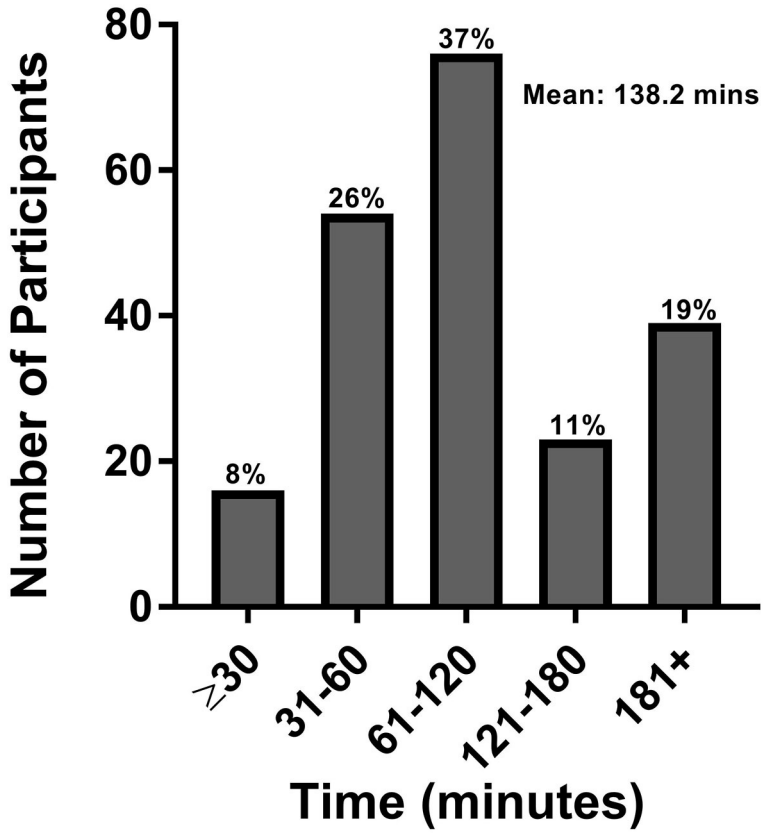

FIGURE 3 | Patient and caregiver commute time. This figure represents the total roundtrip commute time in minutes for patients and caregivers.

$2.38/min for a single visit ($329/138.2 min). There would be additional cost savings for each additional visit, such that that by the fourth visit, the cost would decrease to $0.60/min [($329/138.2 min)/4 visits]. For patients, family members, and payors, investing in a telemedicine device may pay dividends in terms of cost and alleviating burden. In addition, as future studies are undertaken, data on telemedicine cost savings and quality of life improvements for patients with chronic neurologic disability, should strengthen the argument for increased telemedicine utilization in this population.

Study Limitations

Our study is limited by commute time data being derived from patient estimates rather than objectively measured times. More accurate commute times would start from the moment the patient began to physically prepare for a clinic visit, and would include parking time, travel time between parking structure and clinic, clinic registration and visit checkout. But, unlike prior telemedicine studies, we consider not only the time burden of the patient themselves, but other family members/caregivers, who often must accompany a person with disability. Including travel data to multiple clinics and including non-English speakers would provide more generalizable results and including patients without neurological disabilities attending clinic visits may elucidate shared challenges. In addition, the majority of this sample (75%) included individuals living within 25 miles, which may underrepresent the time burden for individuals with neurological disorders that live in rural communities or attend centers with larger catchment areas. Yet, this study was conducted at a regional specialty center of excellence and was composed

TABLE 2 | Barriers to clinic visits.

Difficult to come to clinic	***N* (%)**
Yes	87 (41.8%)
No/not answered	121 (58.2%)
Transport difficulty categories	
Act of transport/arranging transport	31 (35.6%)
Commute time/time spent arranging transportation	24 (27.6%)
Health condition	16 (18.4%)
Parking	15 (17.2%)
Changes to schedule (work, childcare, school, caregiver)	14 (16.1%)
Transport between parking lot and clinic	6 (6.9%)
Cost	2 (2.3%)

N count.

of a large number of participants with a wide range of neurological conditions, which may mediate issues related to the study's generalizability.

CONCLUSION

Telemedicine has the potential to substantially improve time savings for those requiring care for their chronic neurologic disorders. Increased emphasis on telemedicine coverage for those with chronic neurologic disability should be considered by all payors, especially considering the time burden that is placed not only on patients, but also their family members and caregivers who often assist them in attending specialty care visits.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because due to the nature of this study, the participants did not agree for their data to be shared. Requests to access the datasets should be directed to the corresponding author.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements. However, written informed consent was implied via completion of the survey.

AUTHOR CONTRIBUTIONS

DS, BD, KS, and CE shared in the manuscript's concept, design, data acquisition, data analysis, and writing. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.559024/full#supplementary-material

Supplementary Material 1 | Patient questionnaire.

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Telerehabilitation for Word Retrieval Deficits in Bilinguals With Aphasia: Effectiveness and Reliability as Compared to In-person Language Therapy

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Background: Bilinguals with post-stroke aphasia (BWA) require treatment options that are sensitive to their particular bilingual background and deficits across languages. However, they may experience limited access to bilingual clinical resources due to reduced availability of bilingual practitioners, geographical constraints, and other difficulties. Telerehabilitation can improve access to bilingual clinical services for BWA and facilitate the delivery of specific language treatments at distance, but more evidence on its effectiveness and reliability is needed. This study aimed to determine the equivalence of effectiveness and reliability of a semantic treatment for word retrieval deficits in BWA delivered via telerehabilitation relative to in-person therapy.

Methods: We examined the retrospective data of 16 BWA who received 20 sessions of therapy based on semantic feature analysis for word retrieval deficits in person ($n = 8$) or via telerehabilitation ($n = 8$). The two groups were comparable on age, years of education, time of post-stroke onset, aphasia severity, and naming ability in both languages. Treatment effectiveness (i.e., effect sizes in the treated and the untreated language, and change on secondary outcome measures) and reliability (i.e., clinician adherence to treatment protocol) were computed for each delivery modality and compared across groups.

Results: Significant improvements were observed in most patients, with no significant differences in treatment effect sizes or secondary outcomes in the treated and the untreated language between the teletherapy group and the in-person therapy group. Also, the average percentage of correctly delivered treatment steps by clinicians was high for both therapy delivery methods with no significant differences between the telerehabilitation vs. the in-person modality.

Discussion: This study provides evidence of the equivalence of treatment gains between teletherapy and in-person therapy in BWA and the high reliability with which

treatment for word retrieval deficits can be delivered via telerehabilitation, suggesting that the essential treatment components of the intervention can be conducted in a comparable manner in both delivery modalities. We further discuss the benefits and potential challenges of the implementation of telerehabilitation for BWA. In the future, telerehabilitation may increase access to therapy for BWA with varying linguistic and cultural backgrounds, thus, offering a more inclusive treatment approach to this population.

Keywords: bilingual aphasia, telerehabilitation, videoconference, language therapy, semantic feature analysis, reliability, treatment fidelity, treatment effectiveness

INTRODUCTION

Over the last few decades, telerehabilitation has motivated a growing interest across different fields of rehabilitation practice due to its potential to improve accessibility to clinical services for individuals with varying assessment, intervention, and consultation needs. Telerehabilitation entails the use of telecommunications and information technology to provide rehabilitation services at distance (1) and includes videoconference, patient portals or platforms, virtual reality, mobile applications, wearable and therapeutic gaming technologies, and other Internet-based methods that facilitate clinician–patient interactions (2). Telerehabilitation (or telepractice as endorsed by the American Speech–Language–Hearing Association, ASHA, 2020) is particularly relevant to the field of speech and language therapy given its great potential to deliver clinical services via videoconference and through interactive computer-based therapy activities (3) providing a highly suitable method to facilitate language-focused interventions that typically rely on audiovisual interactions (4). Importantly, a recent systematic review of telepractice for adult speech and language pathology services supports its use as an appropriate clinical service delivery model for different adult populations including people with post-stroke aphasia (5) who often experience long-lasting and chronic disability. However, this work also highlights the lack of research examining the benefits and limitations of using telerehabilitation with bilingual adults with post-stroke aphasia (BWA), a clinical population that requires access to bilingual clinicians who can provide high-quality assessment and treatment options that are sensitive to the particular linguistic characteristics and needs that make them different from their monolingual counterparts. To fill this gap in the literature, the present study aims to examine treatment effectiveness and reliability in a semantic-based intervention for word retrieval deficits in BWA delivered via telerehabilitation compared with in-person therapy.

As societies become more multicultural and multilingual, the higher incidence of stroke in older individuals from diverse racial, ethnic, and linguistic backgrounds is expected to result in an increased presence of bilingual adults in neurorehabilitation programs (6). Aphasia is the most common speech and language disorder encountered in bilingual adults after a stroke leading to deficits that may differ across their two languages in terms of the specific language domains affected and their overall severity (7, 8). Word retrieval deficits are a common feature across all aphasic clinical profiles and different patterns of performance and errors in lexical access across the two languages have been described in BWA (9, 10). The effectiveness of in-person speech and language therapy has been largely demonstrated in BWA (11–13), and semantic feature-based treatments targeting word retrieval deficits have often shown significant improvements in lexical access in one or both languages (14–17). However, access to appropriate clinical services for BWA may be often challenging for several reasons.

BWA may seek treatment in their native language because it is essential to communicate with others at home, especially if their degree of physical disability and limited independence after brain insult reduces their social interaction in the dominant language of their local environment (18). Also, bilingual clinical services that offer in-person treatment with the exact language combination demands of BWA may be limited or not readily available. Specialized bilingual outpatient rehabilitation services may be more frequently found in large urban settings (6, 19) compared with small cities or non-urban areas where specific bilingual groups may have lower demographic representation. Furthermore, the availability of trained professional interpreters and translators who assist non-bilingual clinicians might also be restricted to specific bilingual combinations and may vary according to service demand. Clinicians who are located within geographical reach but show low linguistic competency in the patient's two languages may find it difficult to work with BWA who show limited proficiency in the clinician's dominant language and provide appropriate assessments and treatment in the patient's other language (6, 20). Moreover, stroke is a leading cause of acquired disability (21), and stroke survivors present not only language impairments but also deficits in motor function, swallowing, vision, sensation, and cognition (22) that increase their difficulty in managing everyday activities, self-care independence, physical mobility, and participation in language therapy. In addition, several interacting factors that affect both rural and urban dwellers including geographical distance, travel time, transportation, related costs, and availability of caregivers to help patients attend in-person therapy sessions may further minimize the possibilities of BWA to access appropriate rehabilitation services and receive the language therapy they need. Importantly, continued access to clinical rehabilitation services is essential for people with chronic aphasia and reduced availability and limited access to bilingual clinical

services contribute to poor access to health care in bilingual populations (23), which in turn reflects health care disparities that translate into reduced health care outcomes (6).

Telerehabilitation offers a promising approach for delivering language therapy to BWA as it enables the efficient use of rehabilitation resources while overcoming access barriers related to travel distance and shortage of bilingual clinicians for underserved populations (24). In particular, the use of videoconference and Internet-based customized therapy resources may facilitate the delivery of language rehabilitation by allowing clinicians to interact with their bilingual patients in real time, employing linguistically and culturally relevant therapy materials in the targeted language and measuring treatment outcomes in both languages. Research with monolinguals with aphasia addressing different language deficits and rehabilitation approaches has demonstrated the feasibility and benefits of telepractice interventions in this population (5). Moreover, some of these studies have demonstrated that teletherapy addressing word retrieval deficits can lead to significant improvements in lexical access in people with aphasia showing comparable results between videoconference and in-person delivery modalities (25–27). One of these studies has also provided evidence that treatment fidelity, a measure of the reliability with which therapy is consistently provided according to protocol, was equally high across treatment delivery modes (27). Notably, although the literature on teletherapy for bilingual aphasia is rather limited, a recent study with two Mandarin–English BWA has provided initial evidence of the effectiveness of therapy for lexical retrieval deficits delivered via videoconference (28). However, there is a paucity of research on the effectiveness of telerehabilitation for BWA and the reliability with which language interventions are implemented in this modality compared with in-person therapy for this population. Thus, more research is needed to determine whether treatment effectiveness and reliability is comparable across remote and face-to-face language therapy for BWA and to identify the benefits and challenges of teletherapy for this linguistically and culturally diverse population.

The aim of the present study was to determine whether the essential components of a semantic feature analysis treatment for word retrieval deficits in BWA could be delivered with equivalent effectiveness and reliability via telerehabilitation compared with in-person delivered therapy. To this aim, we contrasted (i) treatment effect sizes (ES) and change on secondary treatment outcome measures in the treated and the untreated language and (ii) treatment fidelity conducted by two trained independent bilingual raters on video-recorded treatment sessions across two patient groups, one receiving treatment via videoconference and the other receiving therapy in the in-person modality. We further evaluated inter-rater reliability (IRR) to identify the degree of agreement and consistency between raters on their judgment of clinicians' adherence to treatment procedures.

MATERIALS AND METHODS

Study Design

Our telerehabilitation protocol is part of an ongoing prospective parallel-group, double-blind, phase II randomized controlled trial (RCT) (registered at www.ClinicalTrials.gov, identifier: NCT02916524) that aims to determine the capacity of our computational model BiLex (29) to predict language treatment outcomes in 48 Spanish–English BWA. Briefly, the RCT employs the BiLex model to simulate individual treatment outcomes in each language when treatment is provided in one language (e.g., English) vs. the other (e.g., Spanish). The comparison of these simulated effects allows the model to identify the optimal language for treatment (i.e., English or Spanish) that will lead to maximum therapy benefits across the two languages. Patients are randomly assigned to a model-prescribed experimental group receiving therapy in the optimal language as defined by the computational model, or to a model-opposite control group receiving therapy in the language not prescribed by the model. This randomized patient allocation will enable us to determine whether the computational model is able to identify the optimal language of treatment as reflected by the presence of superior treatment effects in the model-prescribed experimental group relative to the model-opposite control group. All patients receive the same semantic-based language treatment in English or Spanish, and patients who cannot attend in-person therapy sessions can receive therapy in the telerehabilitation modality. Language assessments (i.e., primary and secondary outcome measures) are conducted prior to and after treatment, and each patient receives both assessments and therapy in the same delivery modality (i.e., either in-person or via videoconference). As this is a double-blind RCT, both the researcher conducting the computational simulations that determine the optimal language of treatment for each patient and the clinicians conducting assessments and treatment are blind to each patient's group assignment. The study protocol of our RCT has been fully described and is available elsewhere (30).

It should be noted that the current study involves a retrospective analysis of patients who completed in-person therapy or telerehabilitation if they could not attend in-person assessment and treatment. Because the goal of the RCT is to determine whether the computational model is able to identify the optimal language for therapy, patients were randomized to a model-prescribed experimental group or to a model-opposite control group, instead of being randomly assigned to either treatment delivery modality (i.e., in-person vs. teletherapy). Both the in-person and remote treatments were administered as adherent to the protocol as possible, and the present study examined the effectiveness of teletherapy relative to in-person therapy, and the reliability with which essential treatment procedures were implemented across the two delivery modalities as evaluated by treatment fidelity scores.

Participants

Participants were 16 Spanish–English bilingual speakers (six females, *mean age* = 56.93, *SD* = 17.31, *range* = 24.94–82.44 years; *mean number of educational years* = 14.56, *SD* = 3.08, *range* = 9–19) with chronic post-stroke aphasia (*mean time post stroke onset* = 69.27, *SD* = 104.45, *range* = 2.4–401.12 months). Participants were equally divided into a telerehabilitation group and an in-person therapy group to compare treatment effectiveness (i.e., eight patients in each group) and treatment

reliability (i.e., six patients in each group)[1]. Groups were roughly matched by age, years of education, months post stroke onset, degree of aphasia severity, and overall naming ability in Spanish and English for both comparisons. The participants in the telerehabilitation group received therapy at home via videoconference because they could not attend in-person sessions due to geographic constraints and stroke-related difficulties. The participants in the in-person therapy group attended therapy sessions at one of the recruiting institutions pre-COVID19. In both cases, therapy was conducted by a bilingual clinician with training and experience in providing therapy using both delivery methods in accordance with our established RCT protocol (30). All participants had normal or corrected-to-normal vision and hearing, and demonstrated sufficient ability to understand and follow study procedures. None of them reported a history of psychiatric or neurological illness other than stroke. Participants were recruited via referrals from hospitals, bilingual research and rehabilitation centers, neurologists and speech and language pathologists, or via self-referrals across different locations in the United States including Massachusetts ($n = 6$), California ($n = 4$), Texas ($n = 4$), Rhode Island ($n = 1$), and Washington ($n = 1$). **Table 1** summarizes the demographics of all the study participants.

Ethics Statement

All procedures were reviewed and approved by the Boston University Charles River Campus Institutional Review Board at Boston, Massachusetts (reference number: 4492E). Participants provided their written informed consent to participate in our RCT and to be video-recorded during assessments and treatment regardless of treatment delivery modality.

Assessment of Pre-stroke Bilingual Background

All patients completed the Language Use Questionnaire (31), which provides information about the age of acquisition of the patient's second language (L2) and different metrics known to influence prestroke proficiency in BWA (18) including language use, family proficiency, educational history, lifetime exposure, lifetime confidence, and self-ratings of language ability in English and Spanish (**Table 2**). *Age of acquisition* reflected the age of L2 learning onset. *Language use* measured the proportion of overall time participants and their conversation partners spent using each language on weekdays and weekends. *Family proficiency* evaluated the participants' ratings on their mother, father, and siblings' confidence in using each language expressed as an average proportion across family members. *Educational history* assessed the proportion of usage of each language by the participant and peers across different educational levels including elementary school, high school, and college. *Lifetime exposure* indicated the average proportion of time that participants heard, spoke, and read each language over their lifetime. *Lifetime confidence* measured the participants' average proportion of confidence in hearing, speaking, and reading each language over their lifetime. *Language ability rating* reflected the participants' average self-rated scores of prestroke ability to listen, speak, read, and write in Spanish and English. The LUQ administration was similar across delivery modalities. During in-person administration, the clinician gave the questionnaire to the patient and caregiver and asked them to provide information about the patient's bilingual background in each section described above, directly on the printed form. In the telerehabilitation modality, the clinician shared the LUQ form with the patient and caregiver over via videoconference, asked the questions included in each section of the questionnaire and wrote down their responses on the printed form.

Language Assessments

Assessments were completed following our RCT protocol (30). All participants underwent a comprehensive battery of multiple tests, which were administered separately for each language on alternating English-only and Spanish-only testing sessions to avoid interference between languages. The present study reports the most relevant assessments for the clinical characterization of aphasia and language-processing abilities in our sample. Aphasia severity was determined using the English and Spanish versions of the Western Aphasia Battery—Revised (WAB-R) (32, 33) for patients assessed in person and the validated version of the WAB-R for videoconference (34) for patients in the telerehabilitation modality. Naming ability was assessed using the English and Spanish versions of the Boston Naming Test (BNT) (35, 36) and a 60-item naming screener developed in our laboratory (29), which required patients to name picture exemplars of high-frequency words presented on Microsoft PowerPoint in both languages. Non-verbal semantic knowledge was evaluated with the picture modality of the Pyramids and Palm Trees Test (PAPT) (37). Clinicians followed the standard administration procedures of these tests for patients in the in-person therapy group. For the telerehabilitation group, the clinician shared the test pictures via videoconference and asked the patient to either name the pictures shown on the computer screen (i.e., BNT, 60-item naming screener) or use the mouse to point to the bottom picture that was more related to the top picture (i.e., PAPT). **Table 3** summarizes the clinical aphasia profile and individual scores of our patients on these language assessments prior to and after therapy.

Stimuli

All patients completed the Item Selection Naming Test (ISNT), an extensive picture naming screener developed in our laboratory including 273 words across 13 broad semantic categories with validated semantic features (38). The test was created on Microsoft PowerPoint, and it was administered in each language separately in person or via videoconference following the same procedures described above for other picture naming tests. The test was used to identify items that each patient failed to name correctly in both languages. These items were used to create six 15-word sets including treatment words, untreated semantically related words, and control items in the language chosen for therapy, and their corresponding sets of translations

[1]The number of patients in each group differs across comparisons because treatment reliability was initially planned and completed using a crossed design with $N = 12$ patients; however, four patients were added to the full sample ($N = 16$) over the course of the study to increase statistical power to evaluate treatment effectiveness across delivery modalities.

in the untreated language. All six word sets were included in naming probes administered before, during, and after treatment to evaluate primary treatment outcomes in both languages. A detailed description of the naming probes and related procedures is available elsewhere (30).

TABLE 1 | Demographic background of the bilingual adults with aphasia.

Patient (sex)	Age	Education (years)	Months post onset
Telerehabilitation			
P1 (F)	24.94	16	6.34
P2 (F)	47.2	19	53.15
P3 (M)	44.52	16	19.51
P4 (M)	70.49	12	6
P5 (M)	77.16	19	26.84
P6 (M)	62.73	10	23.85
P7 (M)	68.34	16	244.71
P8 (F)	78.47	11	38.53
In-person therapy			
P9 (F)	27.43	14	48.62
P10 (M)	39.65	13	40.34
P11 (F)	53.89	16	44.45
P12 (M)	82.44	16	401.12
P13 (M)	56.65	9	51.48
P14 (M)	69.31	12	10.32
P15 (F)	54.7	17	58.84
P16 (M)	53	17	37.88

Treatment

All patients received therapy in one language targeting critical semantic features of the targeted trained items (16, 30), which entails retrieving the critical semantic features of the objects targeted in therapy. Treatment comprised 20 sessions in total (i.e., 2-h sessions twice per week). Patients received treatment in person if they were able to attend one of the main recruitment centers, or via videoconference if they were unable to complete in-person sessions due to geographical distance or any other stroke-related difficulties. The protocol was identical whether the treatment was administered in person or remotely, with the adjustments made to remote treatment described later in the Methods section.

All items from the ISNT that could be potentially selected as treatment words in either language, had a maximum of 24 semantic features that were validated for another study (36) by requesting healthy participants to decide whether or not a given feature (e.g., "can fly"; "is a household item") applied to a given word picture exemplar (e.g., "vulture"). The percentage of healthy adults who considered a semantic feature as being applicable or not applicable to a given word during feature validation determined how the feature would be addressed in treatment (i.e., features were treated as applicable if more than 50% of healthy individuals rated it as applicable). In this way, the

TABLE 2 | Prestroke bilingual background of the bilingual adults with aphasia as measured by the Language Use Questionnaire.

Patient	L1[a]						L2						
	Use	Fam	Educ	Exp	Conf	LAR	AoA	Use	Fam	Educ	Exp	Conf	LAR
Telerehabilitation													
P1	0.14	0.75	0.28	0.47	0.65	0.88	5	0.86	0.58	0.72	0.53	0.70	1
P2	0.09	1	1	0.60	1	1	18	0.91	0.17	0	0.40	0.45	0.91
P3	0.01	1	0.5	0.26	0.65	0.66	6	0.99	1	0.5	0.74	0.95	0.86
P4	0.70	1	0.75	0.81	1	1	15	0.30	0	0.25	0.19	0.48	0.88
P5	0.24	1	0.83	0.43	1	0.97	18	0.76	0.42	0.17	0.57	0.36	1
P6	0.66	0.92	0.83	0.67	1	1	16	0.34	0.12	0.17	0.33	0.42	0.83
P7	0.29	1	0.83	0.62	1	0.89	27	0.71	0.25	0.17	0.38	0.47	0.91
P8	0.45	1	0.58	0.54	1	1	10	0.55	0.25	0.42	0.46	0.51	0.97
In-person therapy													
P9	0.37	1	0.56	0.63	0.97	1	11	0.63	0.75	0.44	0.37	0.47	1
P10	0.35	1	0.94	0.76	1	1	21	0.65	0.17	0.06	0.24	0.44	1
P11	0.74	1	0.94	0.59	1	1	3	0.26	0.42	0.06	0.41	0.51	0.74
P12	0.62	1	0.89	0.80	1	1	35	0.38	0.17	0.11	0.20	0.36	0.8
P13	0.75	1	0.75	0.31	0.91	0.86	5	0.25	0.42	0.25	0.69	0.92	0.74
P14	0.25	0.92	0	0.50	0.81	1	3	0.75	0.83	1	0.50	0.97	1
P15	0.55	1	0.89	0.67	1	1	10	0.55	0.25	0.42	0.46	0.51	0.97
P16	0.02	1	1	0.68	1	1	12	0.98	0.08	0	0.32	0.46	1

[a]*Spanish was reported as the native language (L1) for most participants except for P9 (L1 = English). All metrics of bilingual history are expressed as proportions of time spent using a language in a given context (use, lifetime exposure, education history), ability (family proficiency, language ability rating), or confidence (lifetime confidence). Age of acquisition is expressed in years.*

L1, native language; L2, second language; Fam, Family history; Educ, Educational history; Exp, lifetime exposure; Conf, lifetime confidence; LAR, language ability rating; AoA, Age of acquisition.

TABLE 3 | Profile of pre and post treatment scores on secondary treatment outcome measures in the treated and the untreated language in the bilingual adults with aphasia.

	Treated language						Untreated language						NV	
	Aphasia profile (WAB AQ)		BNT		60-Item naming screener		Aphasia profile (WAB AQ)		BNT		60-Item naming screener		PAPT	
Patient	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Telerehabilitation														
P1	Broca (37.3)	**Broca (56.8)**	17	13	17	DNT	Broca (27.3)	**Broca (28.7)**	1	1	0	DNT	42	DNT
P2	Anomic (79.1)	**Anomic (79.9)**	38	36	51	50	Broca (54.4)	**Broca (56.9)**	8	**11**	24	17	49	**51**
P3	Anomic (84.5)	Anomic (84.5)	28	28	34	33	Anomic (89.8)	**Anomic (93.5)**	47	45	47	47	47	**51**
P4	Conduction (57.3)	**Anomic (71)**	22	**26**	31	**37**	Broca (39.8)	**Broca (41.7)**	5	**10**	5	1	48	46
P5	Broca (67.4)	**Conduction (71.7)**	31	31	45	**47**	Broca (64.7)	**Conduction (78.6)**	30	**33**	37	**46**	50	49
P6	Broca (9.6)	Global (7.8)	0	0	0	0	Broca (10.8)	Global (5.2)	0	0	0	0	36	33
P7	Anomic (76)	**Anomic (83.8)**	31	30	40	**45**	Conduction (71.3)	**Conduction (78.8)**	24	17	26	**31**	48	**49**
P8	Conduction (76.8)	**Conduction (80.6)**	24	23	38	**40**	Anomic (78.9)	Anomic (78.8)	27	23	40	37	48	48
In-person therapy														
P9	Anomic (72.3)	**Anomic (74.1)**	14	13	27	23	Broca (66.4)	**Conduction (69.8)**	9	**15**	26	20	42	**43**
P10	Broca (39.5)	Broca (32.9)	3	**4**	11	**15**	Broca (21)	**Broca (32.8)**	4	4	2	**7**	46	45
P11	Conduction (68.8)	**Anomic (79.4)**	24	**26**	30	30	Anomic (90)	**Anomic (93.2)**	54	**55**	56	**59**	51	50
P12	Broca (55.7)	**Broca (56.8)**	8	6	21	DNT	Global (29.6)	**Global (31.9)**	1	1	2	DNT	22	DNT
P13	Anomic (91)	**Anomic (94.3)**	48	48	55	**56**	Anomic (83.2)	**Anomic (89.8)**	18	**26**	29	**31**	48	48
P14	Conduction (46.5)	Conduction (43.3)	11	**15**	6	**17**	Wernicke (33.9)	**Wernicke (36)**	6	6	3	**5**	48	48
P15	Anomic (74.1)	Anomic (74)	22	**28**	19	**35**	Broca's (68.5)	**Anomic (78)**	23	**26**	23	**42**	45	**47**
P16	Wernicke's (51.3)	**Wernicke's (53.9)**	13	**16**	15	**22**	Wernicke's (47.5)	**Wernicke's (53.8)**	4	**12**	11	**19**	46	**48**

Improvement in scores from pre to post-treatment assessments are marked in bold.

NV, non-verbal testing; WAB-R AQ, Western Aphasia Battery-Revised Aphasia Quotient (max. score = 100); BNT, Boston Naming test (max. score = 60); PAPT, Pyramids and Palm Trees (max. score = 52); DNT, Did not test; Pre, Pre-treatment assessment; Post, Post-treatment assessment.

validation of semantic features helped clinicians to guide patients on treatment steps that involved the classification and verification of semantic features for treated words (see Treatment Steps later in this section).

Technical Requirements, Software, and Setup

In both delivery modalities, treatment was conducted on a laptop or desktop computer using the Internet-based Qualtrics survey software available at https://www.qualtrics.com. Twenty Qualtrics surveys were developed for each patient, one per treatment session. Each survey presented 15 treatment items in randomized order in the language chosen for treatment, with one treatment step displayed on the screen at a time (**Figure 1**). Surveys were presented online on the Google Chrome web browser using the Zoom communication software available at https://zoom.us/ to enable video recording of all treatment sessions for reliability analyses and offline scoring of patient responses across treatment steps[2]. The standard Internet connection required followed the Zoom videoconference standard specifications (i.e., broadband wired or wireless 3G or 4G/LTE, with a minimum bandwidth of 600 kbps for up/down). The computer setup required a mouse, microphone, speakers, and a webcam, which could be either a USB plug-in, wireless Bluetooth, or built into the computer. The clinician used an additional computer to access the patient's treatment key designed to provide accuracy feedback for patients' responses in each treatment step, to annotate all verbal responses during therapy, and to score patient responses offline once therapy was completed.

Treatment Steps

In both delivery modalities, a clinician guided each patient throughout six treatment steps emphasizing the semantic feature attributes of each treated item (**Figure 1**). Patients were encouraged to provide responses for each treatment step and were allowed to make corrections to their own responses. No feedback on response accuracy was provided until a final response was obtained from the patient, and only then were responses considered for scoring prior to clinicians' feedback. The six treatment steps were provided as follows.

In step 1 *Naming*, a picture of the treatment item was shown on the screen. Next, the clinician asked the patient to name the item, typed down the response verbatim in the patient's treatment key, and provided verbal feedback (i.e., correct response) regardless of response accuracy. In step 2 *Feature classification*, the treatment item was shown together with a list of 15 semantic features randomly retrieved from a pool of a maximum of 24 features that either applied or did not apply to that item. In step 2A *Feature selection*, the patient was asked to review each feature in the list and transfer the ones that did not apply to that item into the box "feature does not match item" using the computer mouse. Once this step was completed, the clinician provided feedback by explaining why misclassified features required correction and rearranging them such that only the features that applied to the treated item remained in the feature list. In step 2B *Feature assignment*, the patient was asked to classify the features that applied to the treatment item into one of five boxes (i.e., function, characteristics, physical attributes, location, and superordinate category) where they best fit. Once this section was completed, the clinician provided feedback by explaining why misclassified features would best fit a different box and rearranging them into the correct boxes. The survey allowed for clicking on the written features to hear them aloud before moving them into the boxes, which was particularly helpful for patients with reading difficulties. In step 3 *Association*, the treatment item was shown again and the patient was requested to think of something else it reminded them of, or something it was associated with. If the association was not immediately clear, the clinician requested the patient to explain the association and recorded the response and explanation verbatim into the treatment key. In step 4 *Yes/No questions*, the treated item was shown with a list of 15 semantic features randomly retrieved from the entire pool of features validated for that item. The patient was asked to decide whether or not each feature matched that particular item by clicking the "yes" or "no" response options with the computer mouse. This allowed the patient hearing the chosen response for that particular feature read aloud (e.g., *YES to "made of fabric"*). Once all the responses were registered, the clinician provided feedback by making corrections to all incorrect responses and providing an explanation for them. In step 5 *Naming*, the patient saw the picture of the treated word again and was requested to name it. The clinician interventions were similar to step 1. In step 6 *Sentence production*, the patient was asked to create a short sentence with the trained word. Next, the clinician typed down the response verbatim in the treatment key and provided feedback by correcting the sentence into a grammatically and semantically acceptable sentence with the target word.

Treatment Key

An individual treatment key was generated for each patient on a Microsoft Excel spreadsheet consisting of 20 treatment tabs (one per treatment session) including the sequential presentation of all 15 treatment items within each treatment session. **Figure 2** depicts an example of a treatment key with one treatment item for a patient receiving therapy in English. For each treatment item, the treatment key provided the clinician with (i) a list of all the validated semantic features (up to 24 attributes available per item), (ii) a color-coded indication as to whether each feature should be considered applicable or non-applicable for that particular item on the basis of the feature validation ratings mentioned above (treatment steps 2 and 4), (iii) a correct response key to classify each applicable feature as belonging to one or more feature classification boxes including function, characteristics, physical attributes, location, and category (treatment step 2), and (iv) specific fields to manually input the feature classification box selected by

[2]Patients P1, P2, P4, and P6 received therapy using the GoToMeeting software available online at: https://www.gotomeeting.com/ as this was the videoconference platform initially used for this study. However, as the functions "record session," "screen sharing," and "remote control" used in this study are largely comparable between GoToMeeting and Zoom, we only describe the relevant procedures involving the Zoom software.

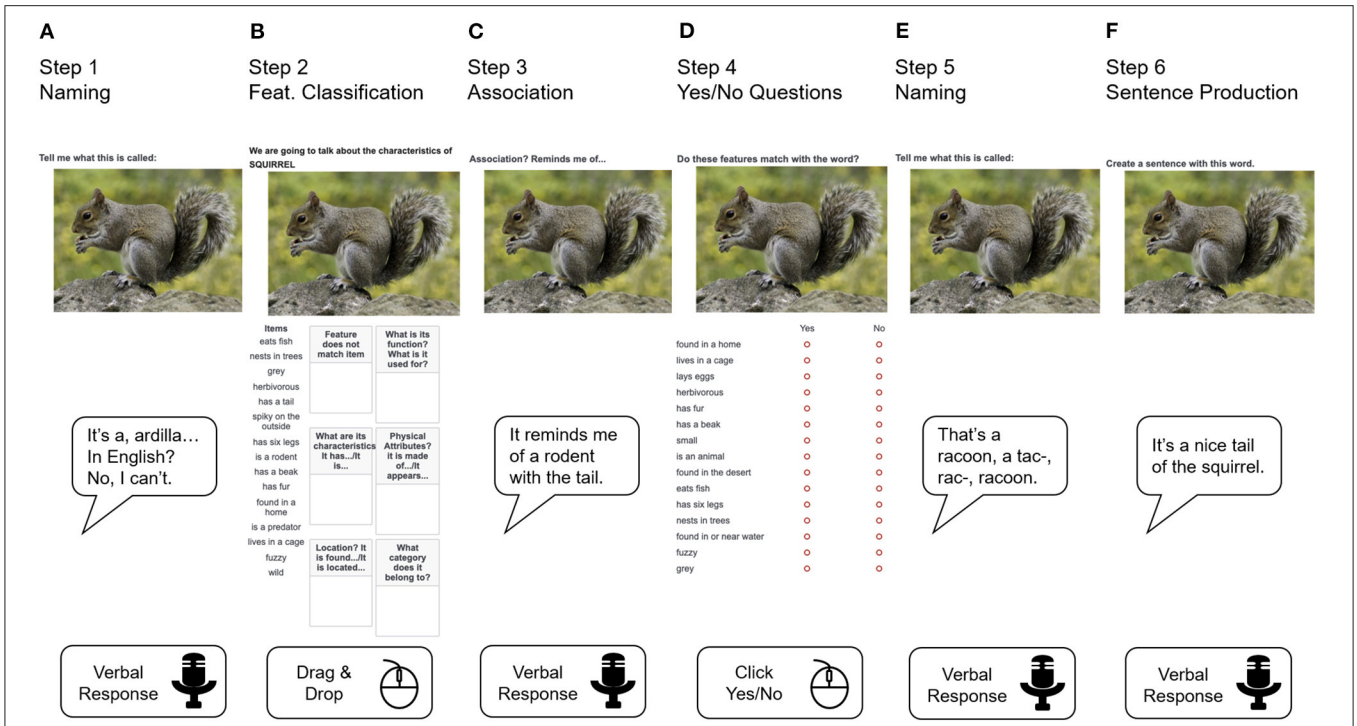

FIGURE 1 | Treatment steps. Example of treatment steps presented across six consecutive screen displays for the treatment item "squirrel." In step 1, the patient provides a verbal naming response for the picture **(A)**. In step 2, the patient drags and drops the semantic features that do not apply to the pictured item into the "feature does not match item" box with the mouse (step 2A) and assigns the remaining features to the other boxes (step 2B) **(B)**. In step 3, the patient provides an association for the item **(C)**. In step 4, the patient decides whether each semantic feature matches the item by clicking on the yes/no options with the mouse **(D)**. In step 5, the patient completes a second naming trial for the picture **(E)**. In step 6, the patient generates a sentence using the treatment word **(F)**.

the patient (treatment step 2), answers to Yes/No questions (treatment step 4), and patient responses to treatment steps involving open questions (treatment steps 1, 3, 5, and 6). In each session, clinicians typed the patient's verbal responses verbatim into the treatment key while performing each treatment step. The scoring of the patient's performance was conducted offline by trained research assistants reviewing videotaped recordings of each session.

In-person Therapy Administration

Both clinician and patient sat in front of a laptop computer in a clinical consulting room at one of the recruitment institutions. First, the clinician started a new session on Zoom and verified that the volume, speakers, front camera, and mouse were working properly. The patient was reminded that the session would be recorded, and the clinician activated the "record" function on Zoom to start video recording the session. Next, the clinician activated the "share screen" function on Zoom to display the Qualtrics survey containing the corresponding treatment session and conducted all treatment steps while recording the patient's verbal and motor responses. The clinician started guiding the patient through all treatment steps (**Figure 1**) while also accessing the treatment key of the corresponding session (**Figure 2**) on another laptop computer to provide accuracy feedback and to input the patient's verbal responses. If the patient was not comfortable using the mouse or was unable to handle it due to hemiparesis, the clinician could control the mouse to generate the patient's response choice for treatment steps that required a motor response. For instance, the clinician could ask the patient to verbally indicate whether or not a given feature should be moved into the "does not apply to this item" box or point to one of the five feature classification boxes where a given applicable feature would best fit it so that the clinician could drag and drop the feature into the selected box (treatment step 2). The clinician could also ask the patient whether or not a feature applied to a treatment item and use the mouse to select the "Yes" or "No" response options for the patient (treatment step 4). Once the session was completed, the recording was stopped and downloaded onto a local computer.

Videoconference Therapy Administration

Clinicians first determined whether a patient would be eligible to receive telerehabilitation at home by requesting information from the patient and caregivers about access to a computer and Internet connection, and patient's ability and comfort with using the computer independently for therapy at home. If the patient was not sufficiently independent to use the computer, clinicians further asked whether the patient's caregiver could help them set up the computer and connect to the Zoom meeting for every treatment session. Patients who did not have a computer at home were offered the possibility of borrowing all the necessary equipment from our laboratory. In this case, the caregiver would

WORD	STEP 2A: FEATURE SELECTION	NO MATCH	ACC	YES	NO	STEP 2B: FEATURE ASSIGNMENT	BOX SELECTED	ACC	STEP 4: YES/NO QUESTIONS	ACC	STEP 1: NAMING			SCORE
squirrel	eats fish*	x	1	0%	100%						patient's response	correct	incorrect	
	found in a home			11%	89%				no	1	it's a… ardilla…. In English? No, I can't.			0/1
	found in or near water*	x	1	16%	84%				no	1				
	found in the desert*	x	1	16%	84%						STEP 3: ASSOCIATION			
	found in the sky*	x	1	0%	100%				no	1	patient's response			
	fuzzy*		1	100%	0%	phys. attributes/ characteristics	phys. attributes	1			it reminds me of a rodent with the tail.			3/3
	grey			95%	5%	phys. attributes/ characteristics								
	has a beak			0%	100%				no	1	STEP 5: NAMING			
	has a tail*		1	100%	0%	phys. attributes/ characteristics	characteristics	1	yes	1	patient's response	correct	incorrect	
	has four legs			74%	26%	phys. attributes/ characteristics					That's a racoon, a tac-, a rac-, racoon.			0/1
	has fur			100%	0%	phys. attributes/ characteristics								
	has hooves*	x	1	5%	95%				no	1	STEP 6: SENTENCE PRODUCTION			
	has six legs*	x	1	0%	100%				no	1	patient's response			
	herbivorous*		1	100%	0%	category	characteristics	0			It's a nice tail of the squirrel.			4/5
	is a mammal			89%	11%	category			yes	1				
	is a predator*	x	1	5%	95%									
	is a rodent*		1	95%	5%	category	location	0	yes	1				
	is an animal*		1	95%	5%	category	location	0						
	lays eggs*	x	1	0%	100%				yes	0				
	lives in a cage			0%	100%				no	1				
	nests in trees*		1	100%	0%	characteristics/ location	location	1						
	small			100%	0%	phys. attributes/ characteristics			yes	1				
	spiky on the outside*	x	1	0%	100%				no	1				
	wild			95%	5%				no	0				
	TOTAL		15/15					3/6		13/15				

FIGURE 2 | Treatment key. Example of a treatment key displaying the treatment word "squirrel" (column 1). The key helps clinicians to document and score patient responses and provide feedback across treatment steps. The 15 out of 24 semantic features randomly presented in a session are marked with an asterisk (column 2). Features that do not apply to the item are color marked according to the percentage of individuals who determined the feature to be applicable or non-applicable during feature validation (columns 5–6). Patient motor responses are collected for treatment steps 2 (columns 3 and 8) and 4 (column 10), and scored for accuracy (ACC; columns 4, 9, and 11) following color-coded indications on whether or not the feature applies to the item (column 3 for step 2A and columns 7–9 for step 4) or the correct response key for feature assignment (column 7). Verbal responses generated during treatment steps 1, 3, 5, and 6 are written down verbatim by the clinician during the session (column 12).

be requested to collect the equipment in person, fill out and sign a checkout form confirming that they would return the equipment at the end of the patient's participation in our study.

Patients who felt confident using the computer and had enough control of the mouse to provide motor responses were sent an email with an invitation to join the Zoom videoconference session and a link to the Qualtrics survey with the appropriate treatment session so that they could set up the Zoom connection and the Qualtrics treatment survey independently. Once connected to the session, the clinician indicated that the video recording would start immediately and requested the patient to share access to their computer screen. This enabled the clinician to see both the participant via the front camera of the computer, and the Qualtrics survey on the participant's computer. The clinician guided the patient through treatment steps while accessing the treatment key on another laptop computer to type down the patient responses and provide feedback. If at any point the patient required assistance, the clinician could request the patient to activate the "remote control" function of Zoom to gain access to the patient's screen and handle the mouse remotely, either to troubleshoot any difficulties or to generate responses for treatment steps 2 and 4 after asking the patient for his or her response choice. The Qualtrics survey had a pre-determined expiration time so that patients with a direct link to the survey would not attempt additional practice once the treatment session was completed.

For patients for whom independent use of the computer was not possible due to motor difficulties or lack of confidence with computer and Internet use, the clinician sent a link to the patient or caregiver via email to join the Zoom videoconference session and opened the Qualtrics survey for the corresponding treatment session directly on his or her local computer. The clinician could then share the computer screen to make the survey visible to the patient, start recording the session, guide the patient across treatment steps, and generate the motor responses for treatment steps 2 and 4 according to the patient response choices while also having the patient visible via the front-camera. Thus, treatment was kept similar across both delivery methods with the only difference that patients in the telerehabilitation modality would receive therapy at home while being connected over videoconference.

Data Management and Confidentiality

Qualtrics surveys collected de-identified data from patients. Zoom video recordings were directly downloaded on the local computer after each session, and they were immediately transferred to the laboratory server, which only the researchers in the study could access. All other personal information and assessment and treatment data were stored and managed using REDCap, a secure web-based software platform designed to support data capture for research studies (39). Qualtrics, Zoom, and REDCap were hosted at Boston University. To ensure privacy and confidentiality, patient electronic data were kept in password-protected computer files, while paper forms and other study materials were kept in physical folders stored in a locket cabinet at Boston University.

Treatment Effectiveness

Treatment effectiveness was evaluated by computing ES for direct treatment effects (i.e., trained items in the treated language) and indirect treatment effects (i.e., untrained translations in the untreated language). ES is a standard measure of the extent to which changes from baseline to after treatment in primary treatment outcomes (i.e., naming probes) are statistically reliable. ES were computed as [(mean of post-treatment probes – mean of baseline probes)/standard deviation of baseline], and defined as

small (4.0), medium (7.0), and large (10.1) ES according to the benchmarks proposed for treatments focused on lexical retrieval (40). In addition, to evaluate treatment effects on secondary outcome measures (i.e., standardized language assessments), we computed treatment-related change scores (post-treatment score – pre-treatment score) for each patient on the WAB-AQ, BNT, 60-item naming screener, and the PAPT in the treated and the untreated language separately.

Treatment Reliability

Treatment fidelity was the measure employed to assess the reliability of the administration of treatment in each modality and the equivalence of procedures delivered across in-person therapy and telerehabiliation. This comparison is important because clinician's behavior during therapy may differ between the remote and face-to-face settings. Treatment fidelity was conducted by two independent fluent English–Spanish bilingual research assistants who used a treatment fidelity scoring form developed for this study to assess clinicians' adherence to treatment procedures (**Supplementary Materials**). The fidelity assessment focused on evaluating the clinicians' behavior during therapy using a specific scoring system that determined whether specific procedures involved in each treatment step were delivered as planned (1 point = fully delivered, 0.5 points = partly delivered, 0 points = not delivered). The scoring system allowed raters to provide partial credit for procedures that were not fully delivered in steps 2 and 4, which required multiple clinician–patient interactions, whereas all other steps could be credited 1 or 0 points as clinician–patient interactions were shorter, and procedures were more straightforward.

The two independent raters received 8 h of training to conduct treatment fidelity assessments. Training included a detailed revision of (i) the manual of treatment steps for clinicians according to our RCT protocol (30), (ii) the treatment fidelity scoring form to evaluate clinicians' adherence to protocol across all six treatment steps, (iii) a troubleshooting form including scoring examples of interventions made by clinicians across treatment steps, and (iv) supervised treatment fidelity scoring of two treatment videos (i.e., four treatment items in total) of two participants included in the RCT but not reported here. In addition, as part of the final calibration step of training, each rater independently scored two 2-h videotaped treatment sessions of these two participants, resolved potential discrepancies between each other in their scoring, and received feedback on their final ratings.

Once training was completed, treatment fidelity was conducted for both treatment delivery modalities separately. Each rater independently reviewed and rated clinician's adherence to treatment steps for six patients (telerehabilitation $n = 3$, in person therapy $n = 3$) on 25% of their videotaped treatment sessions (i.e., five randomly selected videos out of 20 treatment sessions per patient, 30 2-h treatment sessions per rater in total). Treatment fidelity was computed as the percentage of points obtained by clinicians for adherence to protocol procedures across all treatment steps evaluated across the five treatment sessions per patient. Treatment fidelity for the in-person vs. the telerehabilitation modality was then compared using independent samples *t*-tests. Finally, assessing inter-rater reliability (IRR) allows quantifying the degree of agreement and consistency between trained coders who provide independent observation ratings for a set of collected data (41) and is a suggested benchmark to evaluate aphasia treatment fidelity procedures (42). In order to evaluate the degree to which scores were consistent between raters, each independent rater additionally scored 20% of all video recorded treatment sessions initially reviewed by the other rater. IRR was then assessed using two-way mixed, average measures, intraclass correlations (ICCs) for absolute agreement, and we used established cutoffs as reference for the qualitative interpretation of IRR (43) considering it to be poor for values <0.40; fair for values between 0.40 and 0.59, good for values between 0.60 and 0.74, and excellent for values between 0.75 and 1.0.

RESULTS

Between-Group Comparisons on Demographic and Clinical Variables

Patients in the telerehabilitation group ($n = 8$) did not significantly differ from the in-person therapy group ($n = 8$) in terms of their age [telerehabilitation: $M = 59.23$, $SD = 18.71$; in-person therapy: $M = 54.63$, $SD = 16.73$; $t\ (14) = 0.518$, $p = 0.612$], number of years of education [telerehabilitation: $M = 14.88$, $SD = 3.48$; in-person therapy: $M = 14.25$, $SD = 2.82$; $t\ (14) = .395$, $p = .699$], months poststroke onset [telerehabilitation: $M = 51.92$, $SD = 79.59$; in-person therapy: $M = 86.63$, $SD = 127.88$; $t\ (14) = -0.652$, $p = 0.525$], aphasia severity as measured by the WAB-AQ scores in English [telerehabilitation: $M = 55.69$, $SD = 25.32$; in-person therapy: $M = 59.87$, $SD = 22.86$; $t\ (14) = -0.347$, $p = 0.734$] and Spanish [telerehabilitation: $M = 60$, $SD = 27.41$; in-person therapy: $M = 57.22$, $SD = 20.55$; $t\ (14) = 0.229$, $p = 0.822$], naming ability as measured by the BNT scores in English [telerehabilitation: $M = 19.37$, $SD = 15.29$; in-person therapy: $M = 19.12$, $SD = 20.88$; $t\ (14) = 0.027$, $p = 0.979$] and Spanish [telerehabilitation: $M = 22.25$, $SD = 14.16$; in-person therapy: $M = 13.62$, $SD = 7.37$; $t\ (14) = 1.528$, $p = 0.149$], or naming ability as measured by the 60-item naming screener in English [telerehabilitation: $M = 24.25$, $SD = 16.40$; in-person therapy: $M = 23.75$, $SD = 21.16$; $t\ (14) = 0.053$, $p = 0.959$] and Spanish [$M = 30.12$, $SD = 19.58$; in-person therapy: $M = 18.25$, $SD = 10.99$; $t\ (14) = 1.496$, $p = 0.157$] (the same between-group comparisons yielded p values ≥ 0.237 in all cases when only considering the 12 patients included in the statistical analyses comparing treatment reliability between the two delivery modes). These comparisons confirm that the in-person and the telerehabilitation groups were comparable on critical demographic and clinical variables that may influence between-group differences in our treatment effectiveness and reliability analyses.

Treatment Effectiveness Across Delivery Modalities

The results of treatment effectiveness are shown in **Table 4** and **Figure 3**. ES computed for 15 patients was used for the

TABLE 4 | Treatment effectiveness as measured by effect sizes (ES) for the treated language and the untreated language across delivery modalities.

Patient	Treated language	ES treated language (treated items)[a]	ES treated language (control items)[a]	Untreated language	ES untreated language (translations-treated items)[a]	ES untreated language (translations-control items)[a]
Telerehabilitation						
P1	English	9.5	2.51	Spanish	−0.58	0
P2	Spanish	9.33	2.31	English	2.89	0
P3	Spanish	13.28	−1.15	English	4.04	−2.31
P4	Spanish	12.12	1.6	English	1.15	1.73
P5	Spanish	21.94	8.66	English	12.70	4.04
P6	English	NA[b]	NA[b]	Spanish	NA[b]	NA[b]
P7	Spanish	22.52	2.31	English	15.01	1.73
P8	English	13.28	3.46	Spanish	0.58	−0.87
In-person therapy						
P9	Spanish	21.36	−2.31	English	−1.15	−0.58
P10	English	1.73	−1.15	Spanish	−0.58	1.15
P11	Spanish	25.98	3.46	English	21.36	1.73
P12	Spanish	11.55	1.15	English	0	0
P13	English	11.00	4.62	Spanish	1.15	1.73
P14	English	1.00	2.31	Spanish	−0.58	−1.15
P15	Spanish	8.95	1.73	English	−0.29	1.73
P16	Spanish	12.67	1.6	English	10.39	7.33

[a] *Effect sizes defined as small (ES > 4.0), medium (ES > 7.0), or large (ES > 10.1 = large) according to the benchmarks proposed for treatments focused on lexical retrieval (40).*
[b] *NA, Not available. Calculation of ES was not possible for P6 and therefore, this participant was excluded from statistical analyses.*

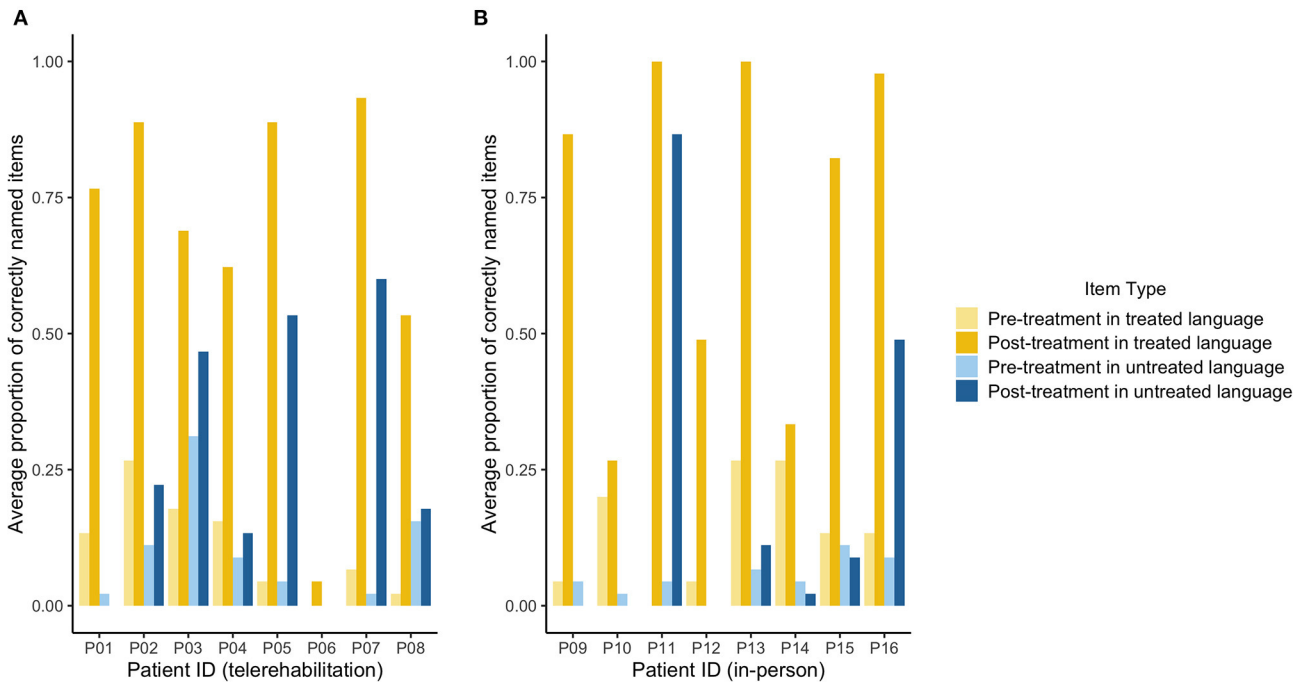

FIGURE 3 | Pre and post treatment naming scores for the telerehabilitation group and the in-person therapy group. The average proportion of correctly named items across three naming probes is shown for treated items (yellow) and untreated control items (blue) prior to treatment (lighter colors) and after treatment (darker colors) for each patient in the telerehabilitation group **(A)** and the in-person therapy group **(B)**.

between-group comparisons of treatment effects reported in this section (ES could not be computed for P6 due to extremely low accuracy in naming probes). The evaluation of direct treatment effects indicated that 13 out of 15 patients demonstrated significant improvement on trained items in the treated language (i.e., ES > 4.0), with three patients showing medium ES (i.e., ES > 7.0) and 10 patients showing large ES (i.e., ES > 10.1). We found no significant differences in ES for treated items in the treated language between the telerehabilitation group (M = 14.57, SD = 5.48) and the in-person therapy group (M = 11.78, SD = 8.62) [t (13) = 0.734, p = 0.476]. The assessment of indirect treatment effects revealed that five out of 15 patients showed significant improvement on translations in the untrained language (i.e., ES > 4.0), with one patient showing a small ES (i.e., ES > 4.0) and four patients showing a large ES (i.e., ES > 10.1), thus showing evidence of cross-language generalization effects in the present sample. Again, there were no significant differences in ES for translations in the untreated language between the telerehabilitation group (M = 5.11, SD = 6.19) and the in-person therapy group (M = 3.79, SD = 8.04) [t (13) = 0.353, p = 0.73]. ES for untrained control items was minimal for most patients in the telerehabilitation and the in-person groups and were within the range of ES reported in previous treatment research with BWA using the same semantic-based intervention (16). Only one patient in the telerehabilitation group showed a medium ES for untreated control items in the treated language and a small ES for their corresponding translations, and two patients in the in-person therapy group showed either a small ES for untreated control items in the treated language or a medium ES for untreated control items in the untreated language (**Table 4**). There were no significant differences in ES for control items in the treated language between the telerehabilitation group (M = 2.81, SD = 2.95) and the in-person therapy group (M = 1.43, SD = 2.26) [t (13) = 1.029, p = 0.322] or in ES for their corresponding translations between the telerehabilitation group (M = 0.62, SD = 2.07) and the in-person therapy group (M = 1.49, SD = 2.61) [t (13) = −0.711, p = 0.49].

All patients except for P6 also showed improvement in at least one secondary treatment outcome measure (**Table 3**). Independent-sample t-tests were conducted to assess differences between the telerehabilitation group and the in-person therapy group on treatment-related change scores (post-treatment score – pre-treatment score) on secondary treatment outcome measures (i.e., WAB-AQ, BNT, 60-item naming screener, and the PAPT). As shown on **Table 5**, there were no significant differences on treatment-related change scores on secondary treatment outcome measures between groups according to treatment delivery modality (all p-values ≥ 0.106).

Treatment Reliability Across Delivery Modalities

The results of the treatment fidelity ratings are shown in **Table 6**. The difference between the average percentage of treatment steps correctly conducted by clinicians according to protocol per patient in the telerehabilitation modality (M = 98.73%, SD =.61%) and in the in-person modality (M = 97.54%, SD = 2.56%) was statistically non-significant [t (10) = 1.103, p = 0.296]. IRR analyses assessing the extent to which our two independent raters agreed on their judgment of clinician's adherence to treatment procedures in each delivery modality further revealed similarly high ICC values of 0.990 [95% CI (0.937–0.999)] for the telerehabilitation modality and of 0.997 [95% CI (0.983–1)] for the in-person modality indicating excellent agreement and high consistency between the two independent raters.

DISCUSSION

The present study aimed to evaluate treatment effectiveness and reliability in a videoconference-delivered semantic feature analysis intervention for word retrieval deficits in Spanish–English BWA compared with in-person delivered therapy, to establish the equivalence of treatment gains, and quality of the delivery of essential components of therapy across delivery modalities. In what follows, we discuss important aspects of the effectiveness and the reliability of telerehabilitation as a treatment delivery model for BWA, and the potential benefits and challenges evidenced in the conduct of this study.

Our study demonstrates that the treatment effects of teletherapy on both the treated and the untreated language are comparable to those observed in the in-person delivery modality while accounting for multiple factors that may influence individual variation in treatment outcomes in BWA. More specifically, direct treatment effects were evidenced by significant improvement on treated items, which achieved predominantly medium and large ES in the treated language for most patients across the two modes of therapy delivery. Cross-language generalization was also evidenced in both groups, although fewer patients demonstrated significant ES in the untreated language, and treatment effects also generalized to untreated control items in the treated or the untreated language for three patients across both delivery modalities. The only patient who did not show improvements in either therapy delivery method was P6, possibly because he was non-fluent in both languages and also showed the highest degree of aphasia severity after stroke. Overall, our findings align with previous research showing positive results for a variety of language interventions via teletherapy for adults with aphasia demonstrating equivalent treatment gains relative to in-person treatment (5) and provide further evidence for the effectiveness of semantic feature analysis-based treatments for word retrieval deficits in BWA (14, 16) regardless of delivery method.

The evidence of direct treatment effects on treated items described above was further supported by the presence of improvements in at least one other secondary treatment outcome measure including aphasia severity (i.e., WAB-AQ scores), naming ability (i.e., BNT and 60-item naming screener scores), and lexical–semantic knowledge (i.e., PAPT scores), which were observed in the treated and the untreated language in both groups. Moreover, treatment-related change scores (i.e., change on post-treatment relative to pre-treatment scores) on these secondary outcome measures did not differ significantly between

TABLE 5 | Comparisons between the telerehabilitation and the in-person therapy groups on treatment-related change scores on secondary outcome measures in the treated and the untreated language.

Secondary outcome measure	Telerehabilitation	In-person therapy	Between-group comparison
WAB-AQ (treated language)	5.54 ± 8	1.19 ± 5.03	t (14) = 1.302, p = 0.214
WAB-AQ (untreated language)	3.62 ± 4.97	5.65 ± 3.56	t (14) = −0.936, p = 0.365
BNT (treated language)	−0.5 ± 2.27	1.62 ± 2.67	t (14) = −1.716, p = 0.108
BNT (untreated language)	−0.28 ± 4.31	3.25 ± 3.57	t (13) = −1.738, p = 0.106
60-item naming screener (treated language)	1.86 ± 2.79	5 ± 6.88	t (12) = −1.12, p = 0.285
60-item naming screener (untreated language)	0 ± 5.48	4.71 ± 7.61	t (12) = −1.330, p = 0.208
PAPT	0.14 ± 2.41	−0.43 ± 1.27	t (12) = −0.277, p = 0.786

Treatment-related change scores were computed as post-treatment score–pre-treatment score on each secondary treatment outcome measure in the treated and the untreated language. WAB-R AQ, Western Aphasia Battery-Revised Aphasia Quotient; BNT, Boston Naming test; PAPT, Pyramids and Palm Trees.

TABLE 6 | Treatment fidelity across the telerehabilitation and the in-person therapy modalities.

Patient	Rater	Number of session scored (1–20)	Treatment steps (max. score)[a]	Treatment steps (actual score)	%Steps correctly delivered
Telerehabilitation					
P1	2	1–8–12–16–18	399	393.5	98.62
P2	2	1–6–10–14–16	476	471.5	99.05
P3	2	3–5–8–17–20	525	521	99.23
P4	1	1–4–9–14–19	186	183	98.38
P5	1	2–6–9–15–20	397	388	97.73
P6	1	4–9–12–15–20	154	153	99.35
In-person therapy					
P7	1	4–7–10–13–19	383	377	98.43
P8	2	8–10–12–16–17	195	192	98.46
P9	2	3–6–11–15–18	308	284.5	92.37
P10	1	3–7–11–13–19	329	327	99.39
P11	2	2–5–7–13–20	483	475	98.34
P12	1	3–5–11–14–17	342	336	98.24

[a] *The total number of scored treatment steps varied across patients despite keeping the number of treatment sessions constant (five sessions per patient) because the treatment was self-paced and each session covered as many treatment items as the patient was able to go through in each 2-h session.*

groups in the treated or the untreated language. These results suggest that treatment effects on secondary outcome measures are comparable across treatment delivery modalities and suggest that far transfer to standardized tests may be possible in both languages subsequent to treatment of specific lexical items, although the extent of these effects may vary across individuals being more likely to occur in treatment responders (44). Thus, the fact that these language assessments were able to capture treatment-related change in both groups, suggests that they could be employed as reliable secondary outcome measures in telerehabilitation for bilingual aphasia.

An important aspect to consider when providing language therapy for BWA via telerehabilitation is the extent to which the main components of an intervention can be implemented with equal quality and accuracy relative to the standard in-person delivery approach. Our analysis of treatment fidelity conducted for both delivery methods showed high clinician adherence to treatment protocol for both delivery modalities and no significant differences in the percentage of correctly implemented treatment steps in the treatment sessions conducted with patients receiving telerehabilitation compared with those receiving in-person therapy. Furthermore, IRR was excellent for both telerehabilitation and in-person therapy, demonstrating high agreement between raters and consistency in their judgment of correct implementation of treatment procedures in the two service delivery modalities. These findings provide evidence that our semantic feature analysis-based treatment for word retrieval deficits in BWA can be reliably implemented by different clinicians via videoconference in a similar manner with comparable quality relative to in-person treatment. Our results are in line with prior research providing evidence that the reliability of treatment for word retrieval deficits in monolinguals with aphasia is similar across the remote and in-person delivery modes (27). Moreover, we suggest that both the development of detailed telerehabilitation treatment protocols and intensive training procedures for clinicians and treatment fidelity raters are crucial to ensure the effective implementation of the intended treatment components and a reliable assessment of treatment

fidelity in clinical rehabilitation research. The evaluation of treatment fidelity is important to improve confidence in the findings of research involving behavioral interventions (45, 46), especially when treatment is provided using less common approaches or delivery methods. While it is important to assess whether clinicians who provide the same treatment to different individuals with aphasia do so in the same way to ensure the validity of the therapeutic effects (47), treatment fidelity has been evaluated inconsistently and infrequently in aphasia intervention studies and RCTs (48, 49), and only a limited number of studies have conducted treatment fidelity on telerehabilitation for adults with aphasia (27, 28). Thus, the present study contributes to the small but important number of studies documenting treatment fidelity in clinical aphasia research and RCTs, and underscores the importance of establishing whether clinician behavior is compliant with treatment protocol across different therapy delivery approaches.

Our study also provides evidence for the practicality and technical usability of teletherapy to deliver semantic feature analysis treatment for word finding deficits in BWA. The Zoom videoconferencing platform enabled clinicians to communicate with patients in real time, provide them with assistance during treatment, and have later access to good quality video-recorded treatment sessions. The Qualtrics software supported successful treatment delivery in the videoconference relative to the in-person modality and clinicians were satisfied with its usability in remote therapy. While Qualtrics was used in the context of synchronous teletherapy based on live clinician–patient interactions, it could also be employed in an asynchronous format based on the offline transmission of patient outcomes (5). The Qualtrics survey parameters are highly customizable in terms of the number of treatment items and semantic features that can be presented per session, which makes them suitable to send the patient home practice assignments and collect additional data on the patient's performance offline. Although not used in this study, its use in the asynchronous teletherapy format could allow examining if self-paced additional exposure and practice with treatment items can further enhance treatment benefits and assess the cost-effectiveness of self-managed computerized therapy (50). Also, the survey can adapt well to different devices including desktop, laptop computers, and tablets allowing patients the flexibility to use the device of their choice as done in other studies (27).

It is also important to consider a few potential implementation challenges for the delivery of semantic feature analysis treatment via telerehabilitation. For instance, patients may differ in the type and amount of assistance needed to access therapy online depending on the degree of their motor impairment. Furthermore, receptive language difficulties may impact the ability of people with aphasia to follow instructions for accessing teletherapy independently (51) making additional training necessary to employ the technology effectively (52). Our treatment setup minimized motor demands by allowing clinicians to facilitate patients' motor responses when needed. Most patients with mild to moderate impairments were sufficiently independent to follow instructions to start the videoconference connection and go through the treatment steps with only minimal remote control support by the clinician (e.g.,: P1, P2, P3, and P5). However, P4 and P6 were more severely affected and needed the support of the clinician and the caregiver, respectively, to set up the computer and videoconference session and complete treatment procedures. Thus, it is possible that videoconference therapy is not fully suitable for patients with severe language and/or motor difficulties, limited experience with technology, and lack of caregiver support. Age is another factor that can negatively impact Internet use, computer literacy, and acceptability of new technology (53, 54). Although we did not conduct a patient satisfaction and acceptability survey after participation, the interaction of older patients with clinicians went smoothly, and all patients regardless of age showed high adherence to treatment, having completed all sessions as planned. It is possible that computer and Internet use via a proxy helped our older and less independent patients gain confidence in this method of treatment delivery and focus on language treatment goals instead of achieving independent computer use. Overall, our findings support the implementation of language therapy for individuals with aphasia in the telerehabilitation modality as shown in previous studies (27, 51, 55, 56), and suggest that videoconference and customized, Internet-based software can facilitate the delivery of semantic feature analysis treatment for BWA via telerehabilitation.

The present study has important implications for bilingual aphasia research and practice. As telerehabilitation is an emerging research field, effectiveness and reliability studies are essential to demonstrate that specific language interventions can be successfully delivered via telerehabilitation and support its potential to overcome access difficulties to bilingual clinical services for BWA. An important goal in bilingual aphasia rehabilitation is to provide optimal therapy for existing language deficits while considering the patient's bilingual background, impairment in the two languages, and patient and family communication needs. However, considering all of these factors in treatment planning for BWA might be restrictive in contexts with limited access to bilingual rehabilitation programs. Indeed, the need to improve limited access to quality rehabilitation services for minorities and underserved bilingual populations has been highlighted in prior research (6, 23, 57). Therefore, evidence that telerehabilitation can be implemented with equivalent effectiveness and reliability for BWA as in conventional in-person therapy can (i) promote its use in clinical practice and inclusion in health insurance coverage, (ii) increase awareness regarding the availability of alternative modes of delivering healthcare resources, (iii) motivate positive attitudes toward teletherapy in patients and caregivers with limited technology knowledge and experience, and (iv) facilitate access to bilingual clinical services for BWA with a variety of cultural backgrounds and language combinations. Validated methods of telerehabilitation may ultimately contribute to reducing health disparities for BWA belonging to cultural and linguistic minorities by increasing their opportunities to equal the standard of care available for monolinguals and minimizing the effects of socioeconomic inequities that may influence their limited accessibility to in-person bilingual treatment clinics.

A few limitations of this work should be considered. This is a retrospective study with a small sample including patients who received teletherapy because they could not attend in-person treatment sessions. Also, in accordance with the goal of our ongoing RCT, patients were randomly allocated to a model-prescribed experimental group or a model-opposite control group instead of using a random assignment according to mode of treatment delivery. Because of the reduced sample size and the retrospective approach of our study, these findings should be considered as preliminary evidence supporting the treatment effectiveness and reliability of teletherapy relative to in-person therapy. However, future research employing non-inferiority prospective clinical trials with larger samples and randomized assignment to each delivery method should be conducted to corroborate these findings.

To conclude, our study findings support the effectiveness and reliability of telerehabilitation as a mode of delivering semantic-based therapy for BWA across different individual profiles of bilingualism and impairment, and recommend its use in the context of clinical trials. As technology evolves to accommodate individuals with language and motor deficits and the use of videoconference to deliver therapy becomes more widespread, telerehabilitation may further show increased potential to provide more linguistic and culturally relevant treatments for this population.

DATA AVAILABILITY STATEMENT

The raw datasupporting the conclusions of this article will be made available upon request to the authors.

ETHICS STATEMENT

The procedures involving human participants were reviewed and approved by Boston University Charles River Campus Institutional Review Board. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

SK conceptualized and designed the study. CP wrote the manuscript and developed the therapy protocols for the study. CP and MS designed all treatment fidelity procedures and conducted the analysis and interpretation of the data. CP, MS, AG, and EC were involved in patient assessment and treatment. NM was in charge of patient randomization and IRB procedures. TG and SS coordinated multisite patient recruitment and data collection. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.589330/full#supplementary-material

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