Study Design | Vol. 8, No. 2 / Apr-Jun 2022 /p. 9-16/ PPCR Journal

Principles and Practice of Clinical Research
A Global Journal in Clinical Research

PPCR
ISSN: 2378-1890

Effect of SpeechVive device on speech intelligibility in Parkinson's Disease patients: A multicenter, phase III, randomized clinical trial protocol

LM. Santana Rodriguez[1], A. Marcinowska[2], C. Go[3], A. Gonzalez[4], GC. Pinto[5], Q. Nai[6], V. Juvvigunta[7], O. Escobar[8], JP. Lima[9], EO. Bedoya-Ismodes[10], M. Mohsin Arshad[11], AC. Benites[12], R. Cuoto[13], A. Perez[14], A. Pavlovic[15], S. Ramos Garcia[16], J. Akram[17], J. Dominguez[18], L. dos Santos[19], W. Zhang[20], M. Feng[21], B. Al-shekh[22], P. Prais Carneiro[23], S. Riccio[24], D. Urla[25], Y. Junqueira[26], JA. Rojas[27], A. Tamayo[28], E. Pichardo[29], L. Mena[30], D. Garcia[31], DS. Schwartz[32]

**Corresponding author: L. M. Santana Rodriguez. Instituto Dominicano de Estudios Virologicos, Santo Domingo, Dominican Republic. Email: laurasantana30@gmail.com.*

Rest of author's affiliation at the end of the manuscript.

Received January 22, 2022; accepted April 5, 2022; published June 16, 2022.

Abstract:

Background: *Hypokinetic dysarthria -with hypophonia as its main symptom- is a common feature of Parkinson's disease, affecting approximately 90% of patients. Hypophonia, characterized by reduced speech volume, leads to difficulties in communication with others due to decreased speech intelligibility. Current treatments involve intensive and cognitively demanding behavioral therapies such as the Lee Silverman Voice Treatment (LSVT). The SpeechVive is a wearable device that produces noise to elicit increased vocal intensity utilizing a natural reflex through the Lombard effect.*

Methods: *We propose a multicenter, phase III, two-armed, parallel, open-label, randomized controlled trial comparing the effectiveness of LSVT with SpeechVive. We seek to assign 238 patients to either LSVT or SpeechVive device in a 1:1 ratio through a stratified permuted block randomization. Patients ages 50 to 80 years, diagnosed with idiopathic Parkinson's Disease based on MDS-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) criteria, a Hoehn and Yahr stage 2 and 3, on stable dopaminergic doses for the past 3 months, with perceived communication difficulties will be included in the trial. Patients will be excluded if they present additional neurodegenerative diseases, prior stroke, laryngeal pathologies, hearing or a severe visual impairment, or who underwent speech therapy or have a deep brain stimulation electrode implanted. The primary outcome is speech intelligibility measured through the Speech Intelligibility Test (SIT) for windows. Secondary outcomes include adherence, the vocal intensity measured with Sound Pressure Level (SPL), Vocal Handicap Index (VIH), and Parkinson's Disease Questionary-39. We will measure each outcome at baseline and after eight weeks of treatment. Our principal statistical analysis is multiple linear regression analysis, with age, gender, site, and PD severity as covariates.*

Discussion: *We present a protocol for a randomized controlled trial addressing an important issue that hampers the ability of Parkinson's Disease patients to communicate effectively. We aim at exploring SpeechVive as an alternative, more accessible treatment for hypophonia in patients with Parkinson's Disease.*

Keywords: *SpeechVive device, Lee Silverman Speech Therapy (LSVT), hypophonia, Parkinson's Disease, the Lombard effect, Speech intelligibility.*

DOI: http://dx.doi.org/10.21801/ppcrj.2022.82.2

Abbreviations:
PD: Parkinson's Disease
LSVT: Lee Silverman Speech Treatment
SLPs: speech and language pathologists
RCT: Randomized Clinical Trial
ENT: otolaryngologists
MDS UPDRS: MDS-sponsored Revision of the Unified Parkinson's Disease Rating Scale
BDI-II: Beck Depression Inventory-II
MMSE: Mini-Mental State Examination
PDQ-39: Parkinson's disease questionnaire 39
SPL: sound pressure level
STI: Speech Intelligibility measured by the Speech Intelligibility Test
VHI: Voice Handicap Index – 10
QOL: quality of life
SI: Summary Index
DMC: Data Monitoring Committee

INTRODUCTION

Parkinson's Disease (PD) is the second most common neurodegenerative disease with an estimated worldwide incidence of 5 to 35 new cases per 100.000 individuals yearly, varying among different countries (Twelves et al., 2003). Up to 90% of individuals with PD will develop speech impairments, and hypophonia is the most prevalent feature (Fabbri et al.,2017; Moya-Gayle & Levy, 2019; Romann et al., 2012), which reduces speech intelligibility, causes difficulties communicating and reduces quality of life (Enderby, 2013; Hammarlund et al., 2018).

The current standard of care for patients with PD hypotonia is speech therapies like the Lee Silverman Speech Treatment (LSVT), where speech and language pathologists (SLPs) instruct patients to increase their speech loudness. However, only 3-4% of speech-impaired PD patients have access to speech therapy programs (Dashtipour et al., 2018; Traila et al., 2005). Moreover, these behavioral speech therapies require close monitoring by a speech therapist, are very intensive, one-to-one therapeutic programs, which require patients to constantly monitor and adjust their level of vocal amplitude when communicating with others.

Previous studies showed that in the presence of background noise, individuals tend to increase their voices (Stathopoulos et al., 2014). This phenomenon is called the Lombard reflex. The novel SpeechVive device draws on the concept of this mechanism; it delivers a background noise that has been shown to make individuals speak louder and clearer by using laryngeal and respiratory mechanisms to increase vocal intensity. (Richardson et al. 2014, Huber et al., 2019; Stathopoulos et al., 2014). Indeed, efficacy studies on the SpeechVive novel device showed promising results (Huber et al., 2019; Stathopoulos et al., 2014). Furthermore, the speech intelligibility tests, administered to patients with hypophonia during the studies which aim to elicit the Lombard effect, documented higher speech intelligibility scores after the treatment (Richardson et al., 2014). Thus, it has been recognized that an increase in speech intensity has an impact on improving speech intelligibility (Adams et al., 2020; Richardson et al., 2014).

Although there are studies that assess the effectiveness of SpeechVive in increasing speech volume (Sadagopan & Huber, 2007, Stathopoulos, et al., 2014) there are no phase III Randomized Clinical Trial (RCT) studies published that compare SpeechVive with current standard of care. This clinical trial compares the effectiveness of SpeechVive with LSVT in increasing speech intelligibility and vocal intensity. Also assess PD patients' adherence and patients' perspective on the functional changes and quality of life (Skodda et al., 2013).

MATERIAL & METHODS

Trial Design

A phase III, multicenter, permuted block randomization with variable sizes, two-arm parallel-group design with an 8-week time follow-up period. This trial was designed according to the SPIRIT statement, to evaluate the effect of SpeechVive on speech intelligibility in Parkinson's Disease patients.

Study Setting

The study will be conducted in hospitals located in urban areas in large cities in the United States with a comprehensive Parkinson's disease management capability in an outpatient setting, neurology departments and rehabilitation centers specialized in Parkinson's voice-related disease with a specialized speech therapist in the field.

Neurologists, otolaryngologists (ENT), and speech therapists would be responsible for gathering the sample population from their patients diagnosed with Parkinson's disease with moderate to severe hypophonia, that meet the inclusion and exclusion criteria

This protocol with the respective informed consent form will be submitted for review and approval by the respective local institutional review boards (IRBs). The ethics approval will therefore be obtained before any research is conducted.

Randomization

A RANDOMIZER (Urbaniak & Plous, 2013) system will be used to randomize patients and distribute them between two groups. Randomization will be demanded by the staff members accountable for recruitment at each center. Subjects will be randomized right after signing the informed consent and those who fulfill the inclusion criteria. The system will use permuted block randomization with variable sizes. Staff will receive, by computer, a number generated by RANDOMIZER, this number will determine patient allocation. The staff gives the number to therapists and then gives the information about treatment allocation to the patient. The therapists can't change the patient's allocation once it has been randomized. During the study, the randomization will be directed by RANDOMIZER to maintain the data organization and the statistician blinded as long as the information is available.

Blinding

Because the intervention (SpeechVive) is a device and the control (LSVT) is a behavioral speech therapy, the blinding of subjects will not be possible in this study. The speech therapists who will analyze the records to define the percentage of intelligibility derived from the Speech Intelligibility Test will be blind. The outcome assessors and the statisticians will be the blinded group and data will be imputed in a controlled system where the assessors will have no access to allocation information. As the study staff and patients will not be blinded, we do not consider an emergency unblinding will be needed considering the patient's safety and wellbeing.

Eligibility Criteria

Inclusion Criteria

The study includes cognitively intact subjects within the age group 50 to 80 who fit the diagnosis of idiopathic Parkinson's disease based on the MDS-sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS UPDRS) criteria and Hoehn Yahr Scale 2-3 (Hoehn & Yahr, 1967), moderate to severe hypophonia (SPL < 65dB), and perceptual difficulty in communication or partner expressing intelligible issues. We selected individuals whose disease had been stable on dopaminergic at least for 3 months to avoid confounding. In case of hearing impairment are included only one ear hearing aid.

Exclusion Criteria

Subjects will be excluded if they have any of the following characteristics: Other neurodegenerative diseases, history of deep brain stimulation, prior strokes, vocal cord or laryngeal pathologies, hearing impairment, more than moderate depression based on Beck Depression Inventory-II (BDI-II) < 24, prior mini-mental state examination (MMSE) < 25 (Yuan-Pang W., et al. 2013), extrapyramidal side effects from a dopaminergic, severe visual impairment that impedes participation in reading to assess communication, non-English speakers, those with less than 7th-grade literacy, and prior speech therapy in the last 2 years. Subjects who are on anticholinergics, cholinesterase inhibitors, and atypical neuroleptics will be also excluded from the study. Patients with Asthma diagnosis or other respiratory problems.

Recruitment

A targeted approach will be used to recruit participants for this trial: recruiting patients from Movement Disorders Centers, Parkinson's Centers, and Support Groups for PD. Initial eligibility screening will be performed by telephone and electronically (medical record), and questionnaire (by internet). Target populations will be initially screened electronically and excluded if they have exclusion criteria. Eligible candidates will receive a phone call for a more thorough face-to-face examination. Face to Face interviews and examinations will be conducted by a neurologist, otolaryngologist (ENT), and speech therapist. During this visit, subjects will be submitted to thorough testing to confirm the absence of severe depression, moderate to severe dementia by Mini-Mental State Examination (MMSE), visual impairment, hearing impairment, and vocal cord dysfunction by a stroboscope. Subjects who have scheduling conflicts will be excluded and so will those who have significant constraints that limited their ability to travel to study sites. Eligible subjects will then present with informed consent.

Adherence

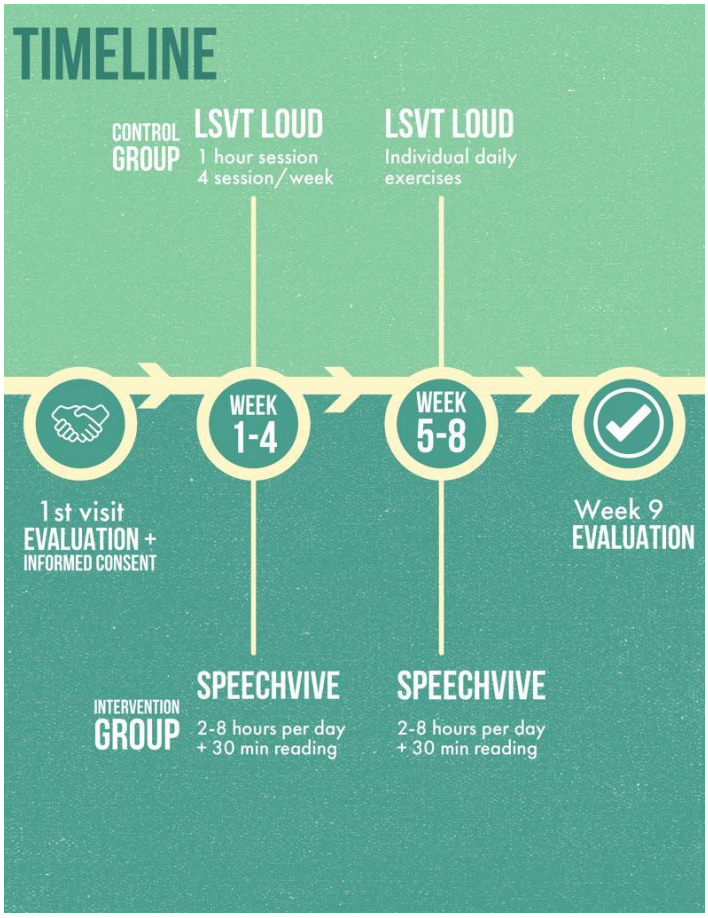
Adherence will be assessed by the analysis of the attendance at the individual speech sessions, the group speech sessions, data collected from the SpeechVive

device, and the participant-reported exercises, according to the interventions. Face-to-face adherence reminder meetings will take place at baseline and a week thereafter. To facilitate adherence to the sessions, expenses such as parking and travel expenses will be reimbursed. Complimentary meal vouchers will be offered.

Also, social adherence-enhancing strategies will be taken, and family members will be involved to promote study participation by providing social support. Research staff will also be trained in adherence-enhancing behavior.

Timeline

The schedule and procedures of this protocol are presented in **Figure 1**.



Interventions

Eligible patients fulfilling the inclusion criteria will be randomized in equal proportions to undergo any of the two interventions:

- SpeechVive device
- LSVT (Lee Silverman Voice Training – LOUD)

Patients randomized to the SpeechVive arm will be asked to use a SpeechVive device obtained and registered by the company. The acquisition of the device is funded by the current grant. SpeechVive is an ear-wearable, safe device, commercially available from authorized SpeechVive suppliers. The device is user-friendly but each participant will be instructed on how to use the device. Patients will be asked to wear the SpeechVive device 3- 8 hours daily for 8 weeks and use it when talking. Patients will also be required to read aloud for approximately 30 minutes daily five days a week using provide materials (SpeechVive website, 2020). Patients can remove the medical device when alone, taking a shower, sleeping, and charging. SpeechVive is charged and stored using the small charging station with the lid.

Patients randomized to the LSVT group will be asked to join and participate in a certified LSVT center. All sessions will be delivered One on One by a certified speech-language pathologist specialized in the LSVT program. The standard LSVT LOUD treatment program spans 4 weeks of individual clinical sessions (4 times per week; 1 hour per session). It highlights high exertion levels and reassures patients to perform at a supreme effort level each session. Standardized tasks are given to the patients such as reading the rainbow passage, doing a monologue, and discussing picture significance and prolonged /a/ to ensure loud phonation during sessions. Likewise, care is given to the respiratory system by reminding patients to take breaths to be loud. In addition to sessions, daily homework and carryover exercises are given.

Once that initial treatment is over, patients will continue to practice at least once a day for 10–15 minutes. A responsible caregiver will be appointed to make sure patients do the required homework.

Modification/discontinuation

Patients will be dropped from the research if the following are met:

- The patient refuses to go on with the research
- Missed 2 sessions of the intervention
- Worsening of the medical condition resulting in hospitalization or death

Outcomes

Primary Outcome

Speech Intelligibility measured by the Speech Intelligibility Test (SIT) for Windows at baseline and after 8 weeks of treatment.

The SIT assesses the sentence-level intelligibility measured in percentage (%) intelligibility and communication effectiveness ratio. The collected speech -samples will be transcribed and assessed perceptually by expert raters blinded to groups (Tamplin et al., 2019). A percentage intelligibility score will be determined by dividing the number of sentences understood by the number of sentences produced (Adams et al., 2008). Transcription has been characterized as an objective intelligibility measure (Miller, 2013; Kent et al., 1989) and involves the listener writing the speaker's message word for word. The word-for-word transcription is then compared with the target production, and the percentage of words correctly transcribed is calculated. SIT for Windows will run under Windows 98/NT/XP/Vista/7, 8, and 10. The SIT is a 32-bit program that will run on 32- and 64-bit versions of Windows (Yorkston, Beukelman & Tice, 2011).

Secondary Outcomes

1. Sound Pressure Level will be considered for constant phonation, reading, picture description, and monologue using the continuously handheld recorder peak SPL Mean vocal SPL measures will be obtained from the PRAAT software program (PRAAT version 6.0; Boersma & Weenik, 2013). Baseline measures of SPL and post-treatment at the 8th week will be obtained.

2. Voice Handicap Index – 10 is a common questionnaire used in a wide range of voice disorders and it is the most applicable subjective self-rating questionnaire in patients who have perceived voice disability. It shows the effect of disabilities resulting from voice handicap on quality of life (QOL) and has been widely used in parkinsonian patients and is included in the movement disorders society speech pathology toolkit. VHI was found to be feasible, reliable, and valid (Guimares 2017). The VHI is scored 0 to mean never up to 4 which means always for the 10 items included. A score of 5 would mean mild handicaps and 33 mean severe handicaps.

3. Quality of Life assessed using the Parkinson's Disease Questionnaire 39 (PDQ-39) assesses how often people affected by Parkinson's experience difficulties across 8 dimensions of daily living including mobility, emotional well-being, activities of daily living, stigma, social support or relationships, bodily discomfort, cognition, and communication (Jenkinson 1997). This is generally a widely accepted scale in research settings for the assessment of the overall quality of life of Parkinson's disease patients (Hagell 2007).

The PDQ-39 Summary Index (SI) is derived by the sum of the eight PDQ-39 scale scores divided by eight (the number of scales), which yields a score between 0 and 100 (100 more health problems). This is equivalent to expressing the sum of all 39-item responses as a percentage score.

The questionnaire can help the health and social care professional to explore the wider impact of Parkinson's on a person's quality of life and can be revisited to detect any changes following treatment or intervention.

4. Adherence: A responsible caregiver will be assigned to make sure treatment is adhered to by the trial participant. Phone calls to check on LSVT patients by the trial center's designated research assistant will be done weekly from the time of enrollment. Phone calls will include discussions on the following matters: Subsequent sessions and Concomitant care. Daily phone calls will be conducted to patients wearing SpeechVive reminding them to use the device. Patients will be allowed to take medications as clinically warranted such as analgesics, antibiotics, and supplements (vitamin C, vitamin A, calcium, multivitamins); vaccines for flu, pneumonia, and covid-19 will be allowed.

Data Management

Electronic capture data will be involved starting from the draft of the data management plan, on regular reviews, and updated up to trial closure. To protect the confidentiality of each subject, numbers will be assigned to each file for the identification of the participants. All data will be entered electronically. If data is printed, this would be kept on file and stored in a secure place accessible only to study team members. A password system will be implemented to ensure secure entries by team members; these passwords would be renewed on each access to the study data. A log sheet would be kept updated, tracking every entry to the system. The data will remain saved for 5 years, later completion of the trial. It is strictly prohibited to use the data archived for any unauthorized purpose or any other research. An interim analysis will not be performed. An independent Data Monitoring Committee (DMC) will be formed to monitor recruitment, patient safety, and the overall conduct of the trial. The composition of the DMC will be that of experts in the field of speech pathology, neurodegenerative diseases, Parkinson's disease, and a

statistician. All will be independent of the investigators and sponsors of the trial.

Sample Size Calculation

Previous studies report a 4% and 6% improvement in the percentage of speech intelligibility after 8 weeks of LSVT and SpeechVive therapy, respectively, with a standard deviation of approximately 5% (Cannito et al., 2012; Richardson et al, 2014). We established an alpha of 0.05, a 1-beta of 0.8, and a dropout rate of 20%, obtaining a sample size of 238 patients, 119 patients per group.

Statistical Analysis for primary and secondary outcomes

We will use STATA 17 version (StataCorp, 2021) to conduct analyses. Baseline characteristics such as age, weight, education years, vital signs, socioeconomic background, comorbidities, and ethnicity will be presented as frequency, mean, medians, and standard deviations, according to if they are categorical or continuous. We will conduct a multiple linear regression to assess the speech intelligibility measured by the Speech Intelligibility Test (SIT) for Windows, Sound pressure level (SPL), VHI, and PD-39 between the two treatment arms (i.e.SpeechVive and LSVT), adjusting by important covariates, namely, age, gender, site, and disease severity.

Missing data

Anticipating missing data, we have incorporated a 10 percent drop out in sample calculation, offering parking and meal vouchers, along with frequent appointment reminders, and using robust exclusion criteria will hopefully prevent higher than normal missing data. We plan to conduct a follow-up survey to understand the reasons for drop-out as adherence is one of our secondary outcomes. We intend to use Intention-to-treat (ITT). For missing data over 5 percent, we intend to complete the data set by using multiple imputations.

DISCUSSION

The decline in the functional communication of PD patients, associated with limited speech intelligibility, is directly related to abnormalities in the area of voice, articulation, and prosody, including loudness (Schulz et al., 2021). Furthermore, central sensory impairments, and difficulties in internal cueing, make these individuals unable to self-regulate the sound level of the voice (Clark et al., 2014; Ho et al., 2000). Low speech intensity referred to as hypophonia, requires treatment (Adams et al. 2005) as this condition progresses over time, contributing to reduced communicative participation, social isolation, and reduced quality of life (Schalling et al., 2017). The SpeechVive device proved to be effective in increasing SPL (Richardson et al., 2014) as well as intelligibility which implies the degree of understanding of a speaker's discrete speech units (sounds, words, sentences) by a listener (Flanagan, 1972). It was also documented that intensive voice treatment speech therapy sessions had a positive effect on the increase of sentence speech intelligibility (Cannito et al., 2012; Levy et al., 2020), word intelligibility (Schulz et al., 2021), and conversational intelligibility (Moya-Gale et al., 2018) among individuals with hypophonia.

This randomized control trial will focus on the comparative analysis of the effectiveness of SpeechVive in relation to the behavioral speech therapy treatment in increasing speech volume and intelligibility scores. The treatment will follow established protocols for LSVT Loud (Miwa & Hwa, 2021), and SpeechVive device guidelines (Huber et al., 2019) ensuring that all participants will receive the same encouragement and positive reinforcement during the study (Schulz et al., 2021).

We need to acknowledge the limitations associated with conducting the intelligibility assessment. While the SIT is a standardized program commonly used, it consists of a sentence- and single- words tasks, assessing the words and sentence-level intelligibility, which may not reflect conversational intelligibility (Tamplin et al., 2019). The perception of speech intelligibility can be affected by individual speaker characteristics, such as gender, voice quality, vocal loudness, articulation impairment, or tiredness (Szulz et al., 2021), thus these factors might influence the results. Similarly, factors related to a listener, such as experience, hearing level, and familiarity with the speaker or speaking task might affect the assessment of speech intelligibility (Rusell, 2013). To ensure the reliability of findings, two independent raters will assess the same speech samples, and interrater reliability will be calculated using intraclass correlation coefficients (Tamplin et al., 2019). Since this is a behavioral intervention study neither the participants, clinicians, nor SLPs can be blinded, therefore they will be made aware of the risk of introducing the bias, and ensure that all interventions are provided with equipoise (Schulz et al., 2021). Measures will be enforced to minimize bias when collecting and assessing the data, and strict

independence will be maintained between clinicians, SLPs, outcome assessors, and statisticians (Schulz et al., 2021). The outcome assessors and statisticians will be blinded.

This study will be the first to provide a comprehensive comparison of the two approaches for the treatment of PD patients with hypophonia. Specifically, this study will assess the capability of each modality in increasing vocal intensity and the improvements in speech intelligibility after each treatment. The present study will also create an opportunity for assessing PD patients' adherence to two treatment groups.

Acknowledgments

We wish to thank the Xplorer's Team members for their contributions, as well as the invaluable support provided by the PPCR team (teaching assistants, faculty members, and coordinators) including Professor Felipe Fregni; without them, this work would not have been possible.

Author affiliations

1 Instituto Dominicano de Estudios Virologicos, Santo Domingo, Dominican Republic.
2 University of Toronto, MSc Fam Med, Toronto, Canada.
3 Jose R. Reyes Memorial Medical Center, Manila, Philippines.
4 Brigham and Women's Hospital, Harvard Medical School, Spain.
5 Universidade de São Paulo, São Paulo, Brazil.
6 Dana-Farber Brigham Cancer Institute, Dana Farber Brigham Cancer Center in clinical affiliation with South Shore Hospital, Boston, United States.
7 University of Nebraska Medical Center, United States.
8 Universidad de los Andes, Bogota, Colombia.
9 Marinha do Brasil, Rio de Janeiro, Brazil.
10 Universidad Peruana de Ciencias Aplicadas, Lima, Peru.
11 Hammad Medical Cooperation, Doha, Qatar.
12 Hospital AC Camargo, São Paulo, Brazil.
13 UNICAMP-Campinas University, Sao Paulo, Brazil.
14 Universidad Francisco Marroquin, Guatemala.
15 Clinica Alemana de Santiago/ Universidad del Desarrollo, Santiago, Chile.
16 Pontificia Universidad Catolica Madre y Maestra, Santiago, Dominican Republic.
17 Hamad Medical Corporation, Doha, Qatar.
18 Pontificia Universidad Catolica Madre y Maestra, Santiago, Dominican Republic.
19 Universidade de São Paulo Faculdade de Medicina de Ribeirão Preto, Brazil
20 Boehringer Ingelheim Pharmaceuticals, Inc, United States.
21 Institute of Diabetes and Obesity, Helmholtz Zentrum Munchen, German.
22 Gulf Laboratory and Radiology Center, Qatar, Doha.
23 Faculdade de Medicina ABC, São Paulo, Brazil.
24 Hospital São Rafael, Salvador.
25 Universidad Francisco Marroquin, Guatemala.
26 Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil.
27 Instituto Tecnologico de Santo Domingo, Santo Domingo, Dominican Republic.
28 Assistant Professor of Neurology, Rady Max School of Medicine, University of Manitoba, Winnipeg Canada
29 Facultad de Ciencias de la Salud, Pontificia Universidad Catolica Madre y Maestra, Santiago, Dominican Republic.
30 Hospital des Clinicas HCFMUSP, Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil.
31 Universidad de San Martin de Porres, Peru.
32 School of Veterinary Medicine and Animal Science (FMVZ), University of Sao Paulo, Sao Paulo, Brazil

Conflict of interests

One of the authors was conducted with the support of a Spain-US Fulbright grant to AGM. The others declare no conflict of interests

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