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The impact of the COVID-19 pandemic on an international rehabilitation study in MS: the CogEx experience

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Title: The impact of the COVID-19 pandemic on an international rehabilitation study in MS; the CogEx experience.

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Trial registration
The trial was registered on September 20th 2018 at www.clinicaltrials.gov having identifier NCT03679468. Registration was performed before recruitment was initiated.

Keywords

Multiple sclerosis, COVID-19, neurorehabilitation, cognition, exercise, multisite, international

Abstract

Pandemic restrictions have led to changes in therapy plans and disrupted rehabilitation services for people with multiple sclerosis. CogEx is an international, multicentre MS dual-intervention (cognitive rehabilitation, aerobic exercise) randomized, controlled rehabilitation trial confined to people with progressive disease. The primary outcome is cognition (processing speed).There are 11 treatment sites in six countries with participants required to make 27 site visits over 12 weeks. Collectively, the large, in-person demands of the trial, and the varying international policies for the containment of COVID-19, might disproportionately impact the administration of CogEx. During the first lockdown, all centres closed on average for 82.9 (SD=24.3) days. One site was required to lockdown on two further occasions. One site remained closed for 16 months. Ten staff (19.2%) were required to quarantine and 8 staff (15.4%) tested positive for COVID. Ten of 264 (3.8%) participants acquired COVID-19. All survived. The mean duration of enrollment delay has been (236.7 (SD=214.5) days). Restarting participants whose interventions were interrupted by the pandemic meant recalculating the intervention prescriptions for these individuals. While the impact of the pandemic on CogEx has been considerable, all study sites are again open. Participants and staff have shown considerable flexibility and resilience in keeping a complex, international endeavour running. The future in general remains uncertain in the midst of a pandemic, but there is cautious optimism the study will be completed with

sufficient sample size to robustly evaluate our hypothesis and provide meaningful results to the MS community on the impact of these interventions on people with progressive MS.

Introduction

To date, the SARS-CoV-2 has infected over 191 million people world-wide of whom 4,101,590 have died (1).There is no current evidence of people with multiple sclerosis (MS) having a higher rate of infection relative to the general population, but the pandemic restrictions have led to changes in therapy plans (2,3) and disrupted rehabilitation services (4). There are also data indicating that the pandemic has disrupted MS research that focuses on rehabilitation and quality of life (5).

CogEx ("Improving cognition in people with progressive MS: a multi-arm, randomized, blinded, sham-controlled trial of cognitive rehabilitation and aerobic exercise study") is an international, multicentre MS dual-intervention randomized, controlled rehabilitation trial funded by the MS Society of Canada. The current published cognitive rehabilitation literature in people with MS has many important limitations. With a few exceptions it is almost exclusively confined to individuals with relapsing-remitting disease. Sample size is typically small with studies lacking the statistical power to support the findings. Data generally come from a single centre raising questions about the broader applicability of the interventions. In many studies, impaired cognition is not a pre-requisite for study inclusion which can dilute the results of the chosen intervention. Furthermore, the overwhelming majority of studies entail a single intervention which means that the potential synergistic benefits of combined interventions have yet to be explored in a systematic way (see Deluca at al., (6) for a comprehensive review of the MS cognitive rehabilitation literature).

Being mindful of these limitations, the CogEx group of investigators designed a study that avoids these potential pitfalls. The methodology has been published elsewhere (7). To summarise, the target sample size of 360 people is confined to people with progressive MS,

making it the largest MS rehabilitation study in this group to date. There are 11 treatment sites across Canada, USA, England, Italy, Belgium and Denmark. The principal investigators, all of whom have long track records of MS research, include neuropsychologists, neurologists, a psychiatrist, physiotherapists, exercise specialists, experts in neuroimaging and statisticians. The study centres encompass general hospitals (with departments of neurology, psychiatry and rehabilitation medicine), and standalone rehabilitation institutes and neurological research and tertiary care centres.

The primary outcome measure is cognition, in particular information processing speed, with ambulation, memory, depression and quality of life as secondary outcomes. A subset of participants undergoes both structural and functional MRI. Participants are randomized into four treatment arms, with biweekly interventions over 12 weeks: aerobic exercise (AE) and cognitive rehabilitation (CR); sham AE and CR; AE and sham CR; and sham AE and sham CR. With blinded assessments undertaken at baseline, 12 weeks and 6 months, participants are required to visit the treatment centre 27 times. The research assistants either administer the interventions or undertake the cognitive and motor assessments. No research assistant completes both tasks. This is to ensure that the testers are kept blind to group membership.

Collectively, the large, in-person demands of the CogEx trial, and the varying international policies for the containment of COVID-19, might disproportionately impact the administration of CogEx. Here, we report data on the impact of COVID-19 on CogEx participants, investigators, and staff.

Method

With the onset of the pandemic, CogEx sites began collecting data relating to number and duration of shutdowns, precautionary measures taken, infection rates in participants and investigators, quarantine rates and COVID-related dropouts and cancellations.

Each study site obtained ethics permission for CogEx. Informed and signed consent were obtained from all CogEx participants.

Results

When the pandemic restrictions began in March 2020, CogEx was a third of the way through recruitment. The effects of the virus and the measures taken to counter it on the study over the past 16 months are shown in Table 1.

Table 1 COVID-19 related data

Event	**N (%)/ mean (SD)**
Treatment centres closed during the first lockdown	11 (100%)
Duration of first lockdown	82.9 (24.3) days
Treatment centres closed during second lockdown	1/11 (9.1%)
Duration of second lockdown (applicable to one site)	33 days
Treatment centres closed during third lockdown	1/11 (9.1%)
Duration of third lockdown (applicable to one site)	64 days
Treatment centres that have not yet reopened	1 (9.1%)
Participants whose interventions were interrupted during first lockdown During weeks 1-3 During weeks 4-9 During weeks 10-12	33 2 21 10
Number of participants who contracted COVID (as of September 9, 2021)	10/264 (3.8%)*
Number of centres in which CogEx staff tested positive for COVID	5/11 (45.5%)
Number of staff who tested positive for COVID	8/52 (15.4%)**
Number of staff who had to quarantine because of exposure to COVID	10/52 (19.2%)
Number of centres reporting screened participants citing COVID concerns for dropping out of the study	11 (100%)
Number of screened participants citing COVID concerns for not enrolling in CogEx	21/574 (3.7%)
Duration of enrollment delays	236.7(214.5) days
Precautions adopted (n=10 sites)*** Sanitize between participants Masking Symptom screening	 10/10 (100%) 10/10 (100%) 10/10 (100%)

Social distancing	9/10 (90%)
Fewer treatment sessions on offer	5/10 (50%)
Temperature check	1/10 (10%)

*Of the 10 people with MS who caught Covid, two were hospitalised but did not require intensive care or ventilation. There have been no long Covid symptoms in any participant.
** All asymptomatic *** One site did not open for 16 months

Discussion

The effects of the pandemic on CogEx have been significant, as demonstrated in the statistics in Table 1. There are, however, more subtle effects that are not shown (MS clinics shutting down and/or reopening to 50% or less capacity) and not known (how many potential participants did not respond to widely displayed flyers advertising the study) which have negatively affected recruitment. In addition, while the study was able to restart in 10 of 11 sites after a three-month shutdown, there was no anticipatory, pre-specified protocol in place for how best to resume the aerobic exercise and cognitive rehabilitation interventions in those participants whose treatment had been interrupted at different time points. Having been caught unaware by the pandemic, and with no precedent to guide our decisions for these specific interventions, we had to reach a decision on how best to restart the study.

To that end the following was decided by consensus amongst all the investigators: if participants were within the first two weeks of their interventions, they would begin the study anew. Participants within the last two weeks of their interventions would be deemed to have completed the study as they would have finished 80% of more of their treatments. For the remaining group, i.e those participants in weeks three through nine inclusive, restarting would entail going back two sessions from their point of interruption. If this did not return subjects to where they had left off in terms of their CR and AE markers, additional make-up sessions were offered to reach these points. Once attained, these participants would complete the remaining weeks of the study. These same principles were applied to participants whose interventions were interrupted by the second and third lockdowns.

The challenges faced by CogEx are to varying degrees shared by other clinical trials that have been active during the pandemic (8,9), although the nature and frequency of our interventions (24 face-to-face supervised treatment sessions in 12 weeks with pre and post assessments within this window along with longer-term follow-up) speaks to the particular intensity of our methodology. To date, the generic challenges faced by clinical trial lists during the pandemic have been addressed by the Food and Drug Administration (FDA) (10) and the Centers for Disease Control and Prevention (CDC) (11). These guidelines were consulted, and where applicable followed, by the CogEx investigators as we devised our restart plans. A recent survey of 87 MS researchers from 18 countries revealed that almost 80% reported additional barriers to research during the pandemic, the two biggest being participant access and interruptions and delays in protocols. Female researchers perceived significantly more barriers compared to other genders (7).

CogEx is a demanding protocol for severely disabled people with MS (median Expanded Disability Status Score to date is 6.0 [IQR: 4.5, 6.5]) and keeping it running during a pandemic, also raised ethical questions. While all centres have been scrupulous in following government, provincial, local health authority and institutional mandates for continuing research, we needed to take into account the potential benefits of the interventions (which are unknown, hence the study) versus the risks to participants and staff of coming into medical institutions that in the majority of sites are also hospitals where COVID-19 patients were being treated. In weighing these competing factors, the investigators were aware that an important driving force behind CogEx is the dearth of rigorous, large scale empirical, multicentre rehabilitation data in people with progressive MS (12–14). Furthermore, the study has been embraced by many of the participants who, historically as a group, have felt overlooked by MS researchers whose attention has focused predominantly on people with relapsing-remitting forms of the disease.

Despite the challenges summarized above, CogEx was able to reboot and at the time of writing has randomized 264 people to the four treatment arms. The core study design and interventions have not changed. To the best of our knowledge, no participant or investigator acquired COVID-19 from the study. The one site that remained closed for the past 16 months has just reopened. As we enter the last third of our study, we are close to being back to full strength in terms of

personnel and clinics being fully opened. Looking to the future, we anticipate that the pandemic will have interrupted the interventions in approximately 10% of our sample. This group does not differ across the four treatment arms. The remaining 90% of participants will all have received their interventions without interruption and there will have been no delay in their timeline for the index- 12-week and 6-month assessments. The 21 screened participants who decided not to begin CogEx because of Covid-related worries had not yet been randomized.

The concerns with respect to the roughly 10% of participants whose interventions were interrupted by the pandemic are these: It is not known whether stopping and restarting the interventions after a delay will lessen the putative benefits of the interventions; how might the delayed timeline influence the outcome in individuals with a progressive disease course and how might being infected with Covid, even if the infection was mild, influence the response to the interventions. To address these questions, when it comes to analyzing the final data set, we will assess these potential confounders by analyzing our data with and without those participants who completed the modified protocol.

However, if we have learned one thing along this challenging journey, it is this: SARS-CoV-2 is here to stay. The vaccine rollout has some ways to go and new waves are predicted as the weather cools in the fall. How societies and medical institutions navigate this in the context of incomplete vaccinations will affect CogEx and our participants too. We are a large, multinational study and our composition is a plus, but during a pandemic, also a minus, given different regional approaches to managing this unprecedented health care challenge.

Faced with these uncertainties, it is helpful to recall what Robert Kennedy said in 1966 on a visit to the University of Cape Town: “Like it or not, we live in interesting times. They are times of danger and uncertainty; but they are also the most creative of any time in the history of mankind”(15)). The SARS-CoV-2 vaccine is proof of the latter. Our hope, in a more modest way, is that CogEx will make a positive difference too in the lives of people with progressive MS.

Declaration

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Conflicts of interest/Competing interest

Anthony Feinstein is on Advisory Boards for Akili Interactive and Roche, and reports grants from the MS Society of Canada, book royalties from Johns Hopkins University Press, Cambridge University Press, Amadeus Press and Glitterati Editions, and speaker's honoraria from Novartis, Biogen, Roche and Sanofi-Genzyme.

Maria Pia Amato received compensation for consulting services and/or speaking activities from Bayer, Biogen Idec, Merck-Serono, Novartis, Roche, Sanofi Genzyme, and Teva Pharmaceutical Industries; and receives research support from Biogen Idec, Merck-Serono, Roche, Pharmaceutical Industries and Fondazione Italiana Sclerosi Multiplav

Giampaolo Brichetto has been awarded and receives research support from Roche, Fondazione Italiana Sclerosi Multipla, ARSEP, H2020 EU Call.

Jeremy Chataway has received support from the Efficacy and Evaluation (EME) Programme, a Medical Research Council (MRC) and National Institute for Health Research (NIHR) partnership and the Health Technology Assessment (HTA) Programme (NIHR), the UK MS Society, the US National MS Society and the Rosetrees Trust. He is supported in part by the National Institute for Health Research, University College London Hospitals, Biomedical Research Centre, London, UK. He has been a local principal investigator for commercial trials funded by: Actelion, Biogen, Novartis and Roche; has received an investigator grant from Novartis; and has taken part in advisory boards/consultancy for Azadyne, Biogen, Celgene, MedDay, Merck and Roche.

Nancy D. Chiaravalloti is on an Advisory Board for Akili Interactive and is a member of the Editorial Boards of Multiple Sclerosis Journal and Frontiers in NeuroTrauma.

Ulrik Dalgas has received research support, travel grants, and/or teaching honorary from Biogen Idec, Merck Serono, Novartis, Bayer Schering, and Sanofi Aventis as well as honoraria from serving on scientific advisory boards of Biogen Idec and Genzyme.

John DeLuca is an Associate Editor of the Archives of Physical Medicine and Rehabilitation, and Neuropsychology Review; received compensation for consulting services and/or speaking activities from Biogen Idec, Celgene, MedRhythms, and Novartis; and receives research support from Biogen Idec, National Multiple Sclerosis Society, Consortium of Multiple Sclerosis Centers, and National Institutes of Health.

Cecilia Meza has no disclosures to report.

Peter Feys is editorial board member of NNR and MSJ, provides consultancy to NeuroCompass and was board of advisory board meetings for BIOGEN.

Massimo Filippi is Editor-in-Chief of the Journal of Neurology and Associate Editor of Human Brain Mapping, Neurological Sciences, and Radiology, received compensation for consulting services and/or speaking activities from Alexion, Almirall, Bayer, Biogen, Celgene, Eli Lilly, Genzyme, Merck-Serono, Novartis, Roche, Sanofi, Takeda, and Teva Pharmaceutical Industries, and receives research support from Biogen Idec, Merck-Serono, Novartis, Roche, Teva Pharmaceutical Industries, the Italian Ministry of Health, Fondazione Italiana Sclerosi Multipla, and ARiSLA (Fondazione Italiana di Ricerca per la SLA).

Jennifer Freeman has been awarded research grants from the NIHR, UK

Matilde Inglese is Co-Editor for Controversies for Multiple Sclerosis Journal; received compensation for consulting services and/or speaking activities from Biogen Idec, Merck-Serono, Novartis, Roche, Sanofi Genzyme; and received research support from NIH, NMSS, the MS Society of Canada, the Italian Ministry of Health, Fondazione Italiana Sclerosi Multipla, H2020 EU Call.

Robert W. Motl has no disclosures to report.

Maria Assunta Rocca received speaker honoraria from Bayer, Biogen, Bristol Myers Squibb, Celgene, Genzyme, Merck Serono, Novartis, Roche, and Teva and research support from the Canadian MS Society and Fondazione Italiana Sclerosi Multipla.

Brian Sandroff has no disclosures to report.

Gary Cutter is a member of Data and Safety Monitoring Boards for Astra-Zeneca, Avexis Pharmaceuticals, Biolinerx, Brainstorm Cell Therapeutics, Bristol Meyers Squibb/Celgene, CSL Behring, Galmed Pharmaceuticals, Horizon Pharmaceuticals,Hisun Pharmaceuticals, Mapi Pharmaceuticals LTD, Merck, Merck/Pfizer, Opko Biologics, OncoImmune, Neurim, Novartis, Ophazyme, Sanofi-Aventis, Reata Pharmaceuticals, Teva pharmaceuticals, VielaBio Inc, Vivus, NHLBI (Protocol Review Committee), NICHD (OPRU oversight committee). He is on Consulting or Advisory Boards for Biodelivery Sciences International, Biogen, Click Therapeutics, Genzyme, Genentech, GW Pharmaceuticals, Klein-Buendel Incorporated, Medimmune, Medday, Neurogenesis LTD, Novartis, Osmotica Pharmaceuticals, Perception Neurosciences, Recursion/Cerexis Pharmaceuticals, Roche, TG Therapeutics. Dr. Cutter is employed by the University of Alabama at Birmingham and President of Pythagoras, Inc. a private consulting company located in Birmingham AL.

Amber Salter is a statistical editor for Circulation: Cardiovascular Imaging.

Data availability Statement:
To promote data transparency, anonymized data will be available upon reasonable request.

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