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Point of view

# Adapting to post-COVID19 research in Parkinson's disease: Lessons from a multinational experience

Eng-King Tan [a,*], Alberto Albanese [b], KRay Chaudhuri [c], Shen-Yang Lim [d], Nicodemus Edrick Oey [a], Christine Hui Shan Chan [a], Yun-Cheng Wu [e], Beomseok Jeon [f], Daniel Truong [g], Werner Poewe [h], Pramod Kumar Pal [i], Louis Tan [a], Puneet Opal [j], Carlo Colosimo [k], H.A. Jinnah [l], Francisco Cardoso [m]

[a] National Neuroscience Institute, Singapore
[b] IRCCS Humanitas Research Hospital, Rozzano, Milano, Italy
[c] Kings College and Kings College Hospital, London, United Kingdom
[d] University of Malaya, Kuala Lumpur, Malaysia
[e] Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, China
[f] Seoul National University Hospital, Seoul, South Korea
[g] University of California, USA
[h] Medical University of Innsbruck, Austria
[i] National Neuroscience Institute of Mental Health and Neurosciences, Bangalore, India
[j] Northwestern University, USA
[k] Azienda Ospedaliera Santa Maria, Terni, Italy
[l] Emory University School of Medicine, USA
[m] Federal University of Minas Gerais, Belo Horizonte MG, Brazil

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With more than 30 million confirmed cases and almost a million deaths, COVID-19 is redefining the way clinical research is being conducted around the world. Lifting of lockdown measures when community spread appeared to have abated has led to resurgence of new clusters, resulting in prompt reinstitution of restrictions such as that experienced in Korea, China, Italy, India, and certain cities in Brazil and the USA. This dynamic back and forth curtailment will likely go on until an effective treatment or vaccine is widely available, necessitating novel adaptations for researchers to continue to thrive worldwide.

For patients with Parkinson's disease (PD), COVID-19 brings forth specific challenges: first, hospitalised PD patients infected with COVID-19 have a higher mortality compared to historic data of hospitalised PD patients in general [1]. Second, PD patients in advanced stages are at a higher risk for pulmonary decompensation [2]. Third, PD patients infected with COVID-19 reported worsening of both motor and non-motor symptoms, requiring medication titration in about 30% of the cases [3]. Fourth, these patients experienced more psychological symptoms and reported poorer quality of life measures such as in measures of anxiety, which is also seen in 60% of their caregivers [4]. Fifth, physical symptoms of PD and COVID-19 such as hyposmia and dysgeusia may overlap, influencing clinical outcomes [5]. Lastly, though general knowledge of COVID-19 exists, more than 80% of PD and 85% of their caregivers do not think there is an association between COVID-19 and PD though a small percentage think there is a higher risk of PD

* Corresponding author. National Neuroscience Institute, Singapore.
*E-mail addresses:* gnrtek@sgh.com.sg (E.-K. Tan), alberto.albanese@unicatt.it (A. Albanese), ray.chaudhuri@kcl.ac.uk (K. Chaudhuri), limshenyang@gmail.com (S.-Y. Lim), nicodemus.oey@gmail.com (N.E. Oey), christine.chan.h.s@sgh.com.sg (C.H. Shan Chan), yunchw@medmail.com.cn (Y.-C. Wu), brain@snu.ac.kr (B. Jeon), dtruong@pmdi.org (D. Truong), werner.poewe@i-med.ac.at (W. Poewe), palpramod@hotmail.com (P.K. Pal), Louis.Tan.c.s@singhealth.com.sg (L. Tan), P-opal@northwestern.edu (P. Opal), c.colosimo@aospterni.it (C. Colosimo), hjinnah@emory.edu (H.A. Jinnah), fecardosoc@gmail.com (F. Cardoso).

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patients contracting COVID-19 [6].

In the face of these challenges, how can we better adapt and implement solutions for clinical research in PD after taking into consideration the community spread and the infrastructure, governance, resources, and priority of individual institutions? Here we share our views and learning experiences in the hope of offering solutions that may potentially help others prepare and adapt to their individual situations depending on the extent of the local community spread.

The common constraints imposed by the pandemic which may affect the integrity of PD and other clinical studies included delays in study enrolment, staffing changes, hiring freezes, coordinator furloughs, limited clinic space, remote interactions due to social distancing measures, manpower shortages due to redeployment of staff to COVID-19-related roles, lack of training to handle infectious disease protocols, and lack of financial support. These challenges and their possible solutions are listed in Table 1. However, while principles in maintaining trial integrity during the COVID-19 pandemic have been proposed [7], they may be challenging for investigators to execute due to the varied nature of clinical studies.

Specific country-to-country restrictions and challenges may differ, and these are highlighted in Table 2. One of the most important issues is the need to justify resuming clinical and pre-clinical studies on PD in the setting of the ongoing pandemic, which depends highly on the COVID-19 disease burden and community spread. Whether or not studies can continue, or have enrolment delayed, or be terminated early will depend on the resources available in the specific jurisdiction and the prevalence of COVID-19 infection of the study locality. The problem can be compounded by unfunded extension of grants and unfinished research or loss of staff. As such, governments and jurisdictions should consider balancing the potential benefits from a particular trial against the possible risks of exposing patients and researchers to COVID-19. As the specific needs of any one clinical trial differs in resource and labour requirement with some drug trials frequently requiring enormous amounts of face-to-face contact between investigators and participants and/or their families, the cumulative risks to COVID-19 exposure differs vastly between studies. We should classify the types of PD studies and rank them in priority and consider the merits of each individual study in

**Table 1**
Challenges for PD research during the COVID-19 pandemic.

| General Challenges | Possible adaptations |
|---|---|
| Research space limitations | Converting physical visits to virtual ones<br>Virtual study monitoring<br>Virtual consent-taking<br>Virtual/remote prescription |
| Manpower shortage | Staggered work hours<br>Split team work model<br>Re-deployment of staff |
| Risk of COVID-19 exposure | Telemedicine for site visits<br>Enforcement of protective equipment<br>Training staff in safe handling of samples<br>Insurance and litigation coverage |
| Data interpretation potentially confounded by COVID-19 | Retraining clinical and research staff on differentiating between COVID-19 symptoms and PD symptoms |
| Potential for cyber security breach | Cyber security training<br>VPN and Firewall implementation/internet separation |
| **Lack of financial support** | Grant extension/variation<br>Postponement of proposal deadlines<br>Changes in objectives/Key Performance Indicators |
| **Lack of training of next-generation researchers** | Advocacy of students<br>Virtual lessons<br>Redirect activities to literature-based and statistical-based research<br>Trainee participation in virtual study visits |
| **Justification of study resumption** | Case-by-case judgment based on clinical priority and COVID-19 disease burden in the area |

**Table 2**
Illustrative examples of restrictions for PD research during reopening period.

| Context and state of affairs | **Restrictions of PD research during transition period between lock down and re-opening** |
|---|---|
| **Singapore**<br>- *Currently in opening transition phase* | Clinical studies in PD restarted after daily community spread dropped to <5%<br>Biospecimen and blood collections for PD are not allowed unless approved under special circumstances and satisfying certain inclusion criteria<br>Neuroimaging for PD research given restricted slots and only during routine patient visits<br>Remote prescriptions are allowed for repeated drugs<br>Audit visits not allowed unless specifically approved in non-clinical areas. |
| **Korea**<br>- *Resurgences are seen with new clusters* | Restriction of entry into the hospital for research subjects and entry allowed only after completion of a screening questionnaire<br>Patients are required to undergo COVID-19 testing to be admitted<br>Lock down measures reinstituted in areas with new clusters of COVID-19 |
| **Italy**<br>- *Has gradually resumed most activities, after moving from the epidemic to the endemic phase* | National policies allow resuming of clinical trials including PD<br>Regional health authorities provide further regulation and hospital authorities define procedures<br>Hospitals limit access to caregivers aiming to reduce overcrowding<br>Telehealth is allowed for clinical studies, but teleprescription is not recognized by law |
| **India**<br>- *COVID-19 cases are still increasing* | Hospitals are primarily focusing on management of COVID-19 patients<br>Patients with PD are discouraged to visit hospitals unless an emergency arises<br>Many patients prefer telemedicine which many hospitals and private practitioners are providing<br>Hospital admission mandate COVID-19 testing<br>Clinical studies in PD have been halted indefinitely (at time of writing) due to lack of staff, patients, insurance and funding, lack of dedicated space and also quarantine issues<br>Government advisory is to temporarily cut down any new research staff recruitment except for essential services<br>Funding for existing research projects have been withheld in most places<br>COVID-19 related research to be given priority |
| **USA**<br>- *COVID-19 cases are still increasing* | Policies and procedures vary by state, and even between institutions in a single state<br>Some areas remain in lockdown for all but "essential" research, while others may continue many research activities<br>The use of telehealth technology is complicated by state-dependent licensing, making it illegal for an investigator or clinician to conduct certain activities with research subjects across state lines |
| **Brazil**<br>- *COVID-19 cases are still increasing* | COVID-19 cases are still increasing<br>Outpatient visits have been limited to people with urgent needs<br>Fast track approval of law allowing nation-based telemedicine visits and remote prescription<br>Substantial number of staff relocated to COVID-19 units in several areas of the |

(*continued on next page*)

**Table 2** (*continued*)

| Context and state of affairs | **Restrictions of PD research during transition period between lock down and re-opening** |
|---|---|
| | country<br>Severe restrictions of access to rehabilitation units |
| **UK**<br>- *Early reopening phase* | Clinical research has resumed with rolling back of lock down measures<br>Insufficient staff to deliver services after restart and no sufficient funding for some crucial survey-based research<br>Research funded by existing grants that were halted can recommence |
| **Malaysia**<br>- *Has gradually resumed most clinical and research activities* | During the strict lockdown period, research subjects e.g., in industry-sponsored drug trials were contacted via phone in place of in-hospital visits, and medicine was dispatched to them<br>Restrictions are gradually lifted during the "recovery movement control order (RMCO)" phase<br>Entry into hospitals is allowed for staff and patients/caregivers only after passing a screening questionnaire, and caregiver numbers are limited in outpatient clinics (only 1 caregiver allowed) and wards, sometimes posing difficulty when collateral history is needed from multiple family members<br>Conferences with max. 200 persons are now allowed, provided SOPs, including physical distancing, are observed. Some hospitals are now looking into starting telemedicine services (for which there was little development previously) |
| **China**<br>- *Early re-opening phase* | Restrictions of entry into the hospital both for the patients and research staff, only after screening questionnaire<br>All clinical trials were stopped before 15 Jul in Beijing, the capital city<br>All patients must undergo the following procedures before admission: (a) epidemiological screening questionnaire; (b) COVID-19 Nucleic acid detection; (c) Chest CT scan; (d) Respiratory tests to exclude other viral pneumonia.<br>Research subjects need to be received and processed separately from general patients<br>Investigators or raters to follow-up and assess the subjects with telemedicine if they are from different provinces or remote cities |

deciding which ones to resume first. For instance, priority should be given to clinical studies with no patient contact (such as telephone survey of quality of life or drug related side effects in PD), studies which can be conducted in non-clinical areas such as a MRI study in an dedicated research scanner, and clinical trials in their passive phase (such as during a drug washout period). When prioritizing which studies should resume first, governing bodies should consider factors such as clinical need eg. where trials of a drug that may potentially slow clinical progression of PD with no other alternative; and novelty eg. where a wearable technology may decrease physical site visits if proven to be a good way to evaluate PD motor symptoms which may justify in-person evaluations even in the face of a pandemic. There will always be scenarios where a PD patient needs to come to hospital for clinical care that cannot be done remotely (such as adjustment of deep brain stimulation parameters, botulinum toxin injections, intravenous infusions, etc.). These patients can potentially be recruited for suitable research studies ad-hoc. The decisions will always be contingent on the epidemiological situation of the locality in question. Over the past months we have learned that this can change very rapidly as we have seen unfold in Australia, Spain, and other countries.

Regardless of the degree of staggered resumption and the complexity of the studies, all efforts should be undertaken to comply to new safety protocols regarding social distancing, protective personal equipment, and minimization of site visits. In several countries including China, Korea, and Singapore, screening questionnaire for COVID-19 needs to be carried out for everyone including clinical trial coordinators and research subjects when they enter the hospital premises. Research staff must be trained in the safe handling of equipment and biological samples: if gastrointestinal or respiratory samples must be taken as part of a trial, a pre-selection clinical screen and case definition should be performed. Cross-institutional trafficking of patients and samples should be kept at a minimum to reduce risk of transmission. Finally, fail-safe measures in the event that a study subject or research team member contracts COVID-19 must be provisioned, such as virtual consent-taking, remote prescription during enforced quarantine, and possibly institution-backed legal recourse (Table 1). Population screening (RT-PCR and/or antibody test) of all asymptomatic individuals including study subjects and research staff for COVID-19 at present is probably impractical, though in some places (such as Italy), testing in healthcare workers in the frontline are frequently carried out.

During the transition period, downscaling of staff numbers, staggering shifts, and converting study visits to a telemedicine focus are possible temporizing measures [8]. For countries which are restarting research studies and may have to deal with reduction in staff numbers, a split team work model can be adopted whereby the research staff gets divided into two teams which operate in a staggered work week (Mon-Wed, Thurs-Fri). In this manner, in line with physical distancing measures, the number of researchers physically present during any moment in time is effectively halved, whilst not affecting the individual researcher's salary. We recognize however that despite the positive emergence of telemedicine [9] and the ingenious use of virtual reality for certain types of PD therapy [10], compliance will be difficult to implement fully on the ground. There are other challenging issues including proper training of patients and staff, availability of remote devices, access to quality broadbands and the medical legal burden of mismanagement and delayed diagnosis of complications especially when multiple comorbidities are present. Furthermore, validated clinical scales to assess PD and complications through remote evaluations are currently not available and hence require further study. On a positive note, the International Parkinson's Disease and Movement Disorders Society (MDS) has launched an initiative to fill this gap due to the large country-to-country differences:in countries such as the USA, state-dependent licensing makes it legally difficult for an investigator or clinician to conduct certain telemedicine activities with research subjects across state lines whereas in China, remote evaluations are possible across different cities. In Italy, telehealth is allowed for clinical studies, but remote prescription is not recognized by law. In Brazil, both medical license and remote prescription are valid throughout the entire national territory.

Finally, perhaps the most practice-changing aspect of post-COVID-19 PD research is the realization that COVID-19 may have specific and profound neurological manifestations [5,6,11,12] [Table 3]. The observation that in addition to vulnerable groups (such as elderly and debilitated subjects), individuals of certain ethnicity (such as Black Africans or Black Caribbeans and Asians) may have increased mortality compared to other races and the incidence and mortality may be compounded by differences in social and other determinants of health [13].

Data interpretation in any PD clinical study has to be handled cautiously as neurological symptoms of COVID-19 may overlap with PD and related disorders and the long-term impact on PD is also unclear. In order to address this, MDS has also developed a web-based repository of movement disorders complications of COVID-19, which will hopefully shed light on the interplay between SARS-CoV-2 and movement disorders (www.movementdisorders.org/COVID-19-Pandemic-MDS/COVID-19-Repository-Submissions.htm).

**Table 3**
Summary of studies on the impact of COVID-19 in PD.

| Study Author & Title | Observations/Learning Points |
|---|---|
| **1) Antonini et al. 2020** [5] *Outcome of Parkinson's Disease patients affected by COVID-19* | Patients of older age with longer disease duration are particularly susceptible to COVID-19 with a substantially high mortality rate (40%)<br>Patients on advanced therapies, such as deep brain stimulation or levodopa infusion therapy, seem especially vulnerable with a mortality rate of 50% |
| **2) Prasad et al. 2020** [6] *Parkinson's Disease and COVID -19: Perceptions and Implications in Patients and Caregivers* | Most patients were not aware that there may be interactions between COVID-19 and PD<br>Amongst the small (8% of patients and 4% of caregivers) who perceived a higher risk of contracting COVID-19, lower immunity and old age were cited as risk factors<br>Problems related to the pandemic were associated with access to healthcare and medication |
| **3) Fasano et al. 2020** [2] *COVID -19 in Parkinson's Disease Patients Living in Lombardy, Italy* | PD patients who contracted COVID-19 were of younger age and associated with chronic obstructive pulmonary disease, obesity, and lower vitamin D compared to controls |
| **4) Kobylecki et al. 2020** [1] *Phenomenology and outcomes of in-patients with Parkinson's disease during COVID-19 pandemic* | Higher mortality rates in hospitalised patients with idiopathic PD during the pandemic period<br>Possible mechanisms of increased mortality: delay in seeking medical attention, lack of service capacity to escalate decompensation in parkinsonism |
| **5) Cilia et al. 2020** [3] *Effects of COVID-19 on Parkinson's Disease Clinical Features: A Community-Based Case-Control Study* | Mild to moderate COVID-19 may be contracted independently of age and PD duration<br>COVID-19 induces worsening motor and nonmotor symptoms of PD<br>Motor symptoms include levodopa-responsive symptoms and increased *off* time, potentially due to inflammatory response and/or pharmacokinetics<br>Non-motor symptoms include increased fatigue, but not cognitive dysfunction or autonomic failure. |
| **6) Shalash et al. 2020** [4] *Mental Health, Physical Activity, and Quality of Life in Parkinson's Disease During COVID-19 Pandemic* | PD patients showed worse stress, depression, and anxiety levels relative to pre-lockdown levels<br>PD patients had a decline in physical activity as measured by the International Physical Activity Questionnaire (IPAQ) scores, which correlated negatively with the Depression, Anxiety, and Stress Scale (DASS) |
| **7) Salari et al. 2020** [12] *Incidence of Anxiety in Parkinson's Disease During the Coronavirus Disease (COVID-19) Pandemic* | PD disease duration did not correlate with severity of anxiety, but severity of anxiety correlated strongly with the fear of getting COVID19<br>PD patients who were concerned about drug availability during the lockdown had higher levels of anxiety |
| **8) Fasano et al. 2020** [11] *Management of Advanced Therapies in Parkinson's Disease Patients in times of Humanitarian crisis: the COVID-19 experience* | Pump-based therapies (ie. Levodopa-carbidopa intestinal gel, apomorphine) can be temporarily converted to oral levodopa<br>Teleconsultations and remote programming can help patients receiving Deep Brain Stimulation therapy |

Until further research is performed to decipher the chronic neurological consequences of COVID-19, investigators must be aware of the fine line between discovering novel therapies for an old disease and preventing complications arising from a new one. The transition to normality is likely to be a challenging as reopening of various economic activities will invariably increase the risk of clusters of outbreaks (as can be seen in Korea, USA, Italy, China and others) that will result in scaling back of research activities yet again. However, the crisis provides an unprecedented opportunity for us to show resilience, and to innovate and adapt to a new normal for PD research in the post-COVID-19 era.

## Contribution statement

TEK and NEO did the first draft and all authors were equally involved in the editing and approval of the final manuscript.

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