BMJ Neurology Open

Future is now: an Australasian perspective on disease-modifying trials in Parkinson's and prodromal disease

Simon JG Lewis ,[1] Carolyn M Sue,[2,3] Antony Cooper,[4] Glenda M Halliday[5]

To cite: Lewis SJG, Sue CM, Cooper A, *et al*. Future is now: an Australasian perspective on disease-modifying trials in Parkinson's and prodromal disease. *BMJ Neurology Open* 2025;**7**:e001070. doi:10.1136/bmjno-2025-001070

Received 10 February 2025
Accepted 05 March 2025

[1]Macquarie Medical School, Macquarie University, Sydney, New South Wales, Australia
[2]Kinghorn Chair, Neurodegeneration, Neuroscience Research Australia, Randwick, New South Wales, Australia
[3]Faculty of Medicine, UNSW Sydney, Sydney, New South Wales, Australia
[4]Garvan Institute of Medical Research, Darlinghurst, New South Wales, Australia
[5]Brain and Mind Centre, Faculty of Medicine and Health, Central Clinical School, University of Sydney, Sydney, New South Wales, Australia

Correspondence to
Professor Simon JG Lewis; simon.lewis@mq.edu.au

ABSTRACT

There is increasing interest in the role of platform trials, where several investigational products targeting disease modification in Parkinson's Disease can be assessed in parallel. Indeed, several initiatives are currently gearing up across North America and Europe to conduct such studies. However, to date, little attention has been paid to ongoing efforts that already exist in Australia and look soon to expand across to New Zealand as part of greater collaboration. This viewpoint will highlight some of these ongoing efforts addressing the challenges and potential solutions for delivering successful studies.

DESIGNING DISEASE-MODIFYING TRIALS FOR PARKINSON'S DISEASE

The Parkinson's disease (PD) field is transitioning into an ever-increasing effort to slow or stop disease progression. Indeed, we read with great interest the recent Gaps and Controversies article from Fabbri *et al*, titled: *Advantages and Challenges of Platform Trials for Disease Modifying Therapies in Parkinson's Disease*.[1] The authors helpfully summarised some of the major challenges confronting the field of disease-modifying trials in PD and explored the advantages, challenges and potential solutions offered by platform trials. Emphasis was given to the importance of disease heterogeneity, genetic factors and pathological mechanisms (eg, urate levels, neuroinflammation) when enrolling participants depending on the trial's main objective. The paper concluded that platform trials, which enable the simultaneous testing of multiple drugs under one Master Protocol, represent an attractive strategy to address the urgent need for identifying treatments capable of slowing PD.

The authors reported on several proposed initiatives including the Edmond J. Safra Accelerating Clinical Trials in PD that draws together significant expertise from a variety of stakeholders across the UK; the North American Pathway to Prevention platform that is seeking to develop cohorts of 'at-risk' individuals with either a genetic predisposition or recognised premotor features (hyposmia and Rapid Eye Movement Sleep Behaviour Disorder (RBD)); the French NS-Park Master Trial and two Norwegian initiatives (SLEIPNIR and HYDRA) that are yet to finalise their protocols. We would like to thank the authors who also touched very briefly on the work of the Australian Parkinson's Mission (APM), which to the best of our knowledge, is the only platform initiative that is currently active with trials running since 2020. Here, we would like to expand on the current state of the APM, which was kindly supported by a Medical Research Future Fund grant from the federal government (GA39194), along with other ongoing efforts in Australasia.

ONGOING PLATFORM TRIALS

The APM has already commenced two phase II multiarm platform trials that are evaluating several repurposed investigational products in one overarching double-blind protocol, which broadly follows the original phase II trial evaluating Exenatide[2] with a 48-week treatment period, followed by a 12-week washout. The first of these trials (APM001—ACTRN12620000560998) is evaluating three agents against a common placebo: (1) albuterol—a beta2-adrenoreceptor that regulates the alpha-synuclein gene[3]; (2) alogliptin—an inhibitor of dipeptidyl peptidase 4 that creates a sustained increase in the blood levels of two natural incretins (glucagon-like peptide 1 and gastro-intestinal peptide), which both act as neuroprotective hormones[4] and (3) nilvadipine—a calcium channel blocker that has anti-inflammatory properties.[5] The APM001 trial involves eight Australian centres and completed recruitment in early 2024, screening over 200 participants with established PD on dopaminergic treatment. The second APM trial (APM002—ACTRN12623000843651) began recruitment in early 2024 and is also running across eight

Australian sites with the aim of recruiting around 240 participants. The APM002 trial is evaluating the potential benefits of the antimicrobial doxycycline and the expectorant ambroxol as monotherapies and in combination with each other, against a common placebo. Preclinical work has shown that doxycycline reshapes α-synuclein oligomers into off-pathway species that do not evolve into fibrils,[6] while ambroxol can enhance the enzymatic activity of both wild-type and mutant glucocerebrosidase (GCase).[7 8] Critically, there is a bidirectional and reciprocal effect between GCase activity, a lysosomal enzyme, and the levels of α-synuclein that drives α-synuclein pathology.[9] Lower levels of GCase promote the accumulation of α-synuclein,[10] and higher concentrations of α-synuclein lead to a further reduction in GCase levels.[11] It should be highlighted that even in patients who do not exhibit any *GBA1* gene mutations, there are reduced levels of GCase activity,[12 13] offering a potentially druggable target.

Both of the current APM trials have adopted a 'pathways' approach, where multiple investigational products targeting different pathophysiological pathways are being tested in parallel, in the same protocol, allowing the fastest approach for determining their potential benefit.[14 15] This 'smart trial' design also benefits from testing novel blood biomarkers that can assess target engagement (eg, neuroinflammation, incretin levels) and potentially disease response by evaluating biomarkers that have been shown to correlate with disease severity in PD (eg, GCase activity,[16] neurofilament light levels).[17] The protocol, by randomising cases based on their baseline disease severity as measured by section III of the Movement Disorders Society Unified PD Rating Scale, also seeks to avoid some of the issues that have been seen in similar trials.[2] In addition, both APM trials will allow for a precision medicine approach by conducting detailed genotyping in all participants. Furthermore, APM002 also randomises all subjects at baseline by calculating a polygenic risk score for a custom model designed for the drugs being tested. The APM studies will also benefit from the ability to perform the recently described detection of pathogenic α-synuclein seeds from serum samples.[18]

OPERATIONAL FRAMEWORKS

The APM represents a collaboration between academic institutions (Macquarie University, University of Sydney, Garvan Institute) and not-for-profit, patient-focused organisations (Parkinson's Australia, Shake it Up Australia, Cure Parkinson's UK). The APM would like to acknowledge the efforts of Cure Parkinson's UK who, through the international Linked Clinical Trials initiative, were able to identify many of the repurposed medications that have been included in our platform trials.[19] To address the organisational issues raised by Fabbri *et al*, we have established a successful governance framework with Steering and Scientific Research Committees and have identified one academic institution to operate as the Sponsor. Our methodological approach has allowed us to maintain blinding and strengthen randomisation. Given that we are using these phase II trials to identify a signal, we are not limited statistically by our design, as we are not looking to compare the effect of the different active arms in our trials. Significantly, our trials benefit from having the same protocol across studies, which might even allow us to combine our placebo arms in future and potentially dispense with a Control group moving forward, assuming that we can maintain the same framework. The design of the APM002 trial has also facilitated the combination of multiple drugs to counteract disease mechanisms simultaneously. Finally, these national efforts have triggered the evolution of a wider Australasian clinical trials network for Movement Disorders coordinated by its national professional society (MDSANZ) in partnership with not-for-profit stakeholders and community groups.

PRODROMAL SYNUCLEINOPATHY TRIALS

In addition to ongoing trials for PD, we would also like to highlight that Australia is already undertaking a disease-modifying trial in patients with isolated REM sleep behaviour disorder (iRBD), the prodrome for both PD and dementia with Lewy bodies.[20] It has been proposed that neuroinflammation may act as a driver for these synucleinopathies, which could make it a suitable target for neuroprotective strategies.[21] Previous positron emission tomography (PET) studies in patients with iRBD have shown increased levels of neuroinflammation[22–24] that can be correlated with progressive dopaminergic loss over a 3-year period.[25] Supported by funding from a Parkinson's UK Drug Discovery and Development Programme grant, we are already conducting a phase IIa, randomised, double-blind, placebo-controlled study to investigate the safety and efficacy of PXS-4728A in partnership with Syntara (NCT05904717). This product demonstrates a reduction of neuroinflammation in a preclinical model and has been shown to be safe in humans. Around 40 participants with iRBD will be recruited from centres at Macquarie University, Sydney and the University of Oxford. Participants will receive either active drug or matching placebo in a ratio of 3:1 for a period of 12 weeks, followed by a 12-week washout period. The primary outcome will be a within-subjects analysis of microglial PET imaging in those subjects in the active arm with a range of exploratory outcomes looking at safety and other inflammatory biomarkers (cerebrospinal fluid and blood).

THE FUTURE IS NOW…

Given these ongoing efforts in both PD and prodromal disease, we would argue that Australasia has successfully entered a period of disease stratification and multiarm trials, which might offer the potential to be adaptive. However, the incorporation of multistage decision points will depend on the development of robust biomarkers

that are sensitive to changes in disease progression in the timeline of the trial. We would emphasise that further collaborative efforts are urgently required, especially with a view to increasing global diversity. As demonstrated recently, ethnic variance must not be ignored in PD,[26] and there should be greater efforts to include international centres in future trials that would facilitate the recruitment of under-represented populations.

X Simon JG Lewis @profsimonlewis

Contributors SL generated the first draft and CMS, AC and GMH critically reviewed the manuscript. No AI was used in the preparation of this manuscript.

Funding This study was funded by the Medical Research Future Fund (GA39194).

Competing interests No, there are no competing interests.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; internally peer reviewed.

ORCID iD

Simon JG Lewis http://orcid.org/0000-0002-4093-7071

REFERENCES

1 Fabbri M, Rascol O, Foltynie T, *et al*. Advantages and Challenges of Platform Trials for Disease Modifying Therapies in Parkinson's Disease. *Mov Disord* 2024;39:1468–77.
2 Athauda D, Maclagan K, Skene SS, *et al*. Exenatide once weekly versus placebo in Parkinson's disease: a randomised, double-blind, placebo-controlled trial. *Lancet* 2017;390:1664–75.
3 Mittal S, Bjørnevik K, Im DS, *et al*. β2-Adrenoreceptor is a regulator of the α-synuclein gene driving risk of Parkinson's disease. *Science* 2017;357:891–8.
4 Kim NH, Yu T, Lee DH. The nonglycemic actions of dipeptidyl peptidase-4 inhibitors. *Biomed Res Int* 2014;2014:368703.
5 Morin A, Mouzon B, Ferguson S, *et al*. Treatment With Nilvadipine Mitigates Inflammatory Pathology and Improves Spatial Memory in Aged hTau Mice After Repetitive Mild TBI. *Front Aging Neurosci* 2018;10:292.
6 González-Lizárraga F, Socías SB, Ávila CL, *et al*. Repurposing doxycycline for synucleinopathies: remodelling of α-synuclein oligomers towards non-toxic parallel beta-sheet structured species. *Sci Rep* 2017;7:41755.
7 Ivanova MM, Changsila E, Turgut A, *et al*. Individualized screening for chaperone activity in Gaucher disease using multiple patient derived primary cell lines. *Am J Transl Res* 2018;10:3750–61.
8 Mullin S, Smith L, Lee K, *et al*. Ambroxol for the Treatment of Patients With Parkinson Disease With and Without Glucocerebrosidase Gene Mutations: A Nonrandomized, Noncontrolled Trial. *JAMA Neurol* 2020;77:427–34.
9 Tayebi N, Walker J, Stubblefield B, *et al*. Gaucher disease with parkinsonian manifestations: does glucocerebrosidase deficiency contribute to a vulnerability to parkinsonism? *Mol Genet Metab* 2003;79:104–9.
10 Mazzulli JR, Xu Y-H, Sun Y, *et al*. Gaucher disease glucocerebrosidase and α-synuclein form a bidirectional pathogenic loop in synucleinopathies. *Cell* 2011;146:37–52.
11 Gegg ME, Burke D, Heales SJR, *et al*. Glucocerebrosidase deficiency in substantia nigra of parkinson disease brains. *Ann Neurol* 2012;72:455–63.
12 Atashrazm F, Hammond D, Perera G, *et al*. Reduced glucocerebrosidase activity in monocytes from patients with Parkinson's disease. *Sci Rep* 2018;8:15446.
13 Murphy KE, Halliday GM. Glucocerebrosidase deficits in sporadic Parkinson disease. *Autophagy* 2014;10:1350–1.
14 McFarthing K, Rafaloff G, Baptista MAS, *et al*. Parkinson's Disease Drug Therapies in the Clinical Trial Pipeline: 2021 Update. *J Parkinsons Dis* 2021;11:891–903.
15 Foltynie T, Gandhi S, Gonzalez-Robles C, *et al*. Towards a multi-arm multi-stage platform trial of disease modifying approaches in Parkinson's disease. *Brain* 2023;146:2717–22.
16 Hughes LP, Pereira MMM, Hammond DA, *et al*. Glucocerebrosidase Activity is Reduced in Cryopreserved Parkinson's Disease Patient Monocytes and Inversely Correlates with Motor Severity. *J Parkinsons Dis* 2021;11:1157–65.
17 Youssef P, Hughes L, Kim WS, *et al*. Evaluation of plasma levels of NFL, GFAP, UCHL1 and tau as Parkinson's disease biomarkers using multiplexed single molecule counting. *Sci Rep* 2023;13:5217.
18 Okuzumi A, Hatano T, Matsumoto G, *et al*. Propagative α-synuclein seeds as serum biomarkers for synucleinopathies. *Nat Med* 2023;29:1448–55.
19 Brundin P, Wyse RK. The Linked Clinical Trials initiative (LCT) for Parkinson's disease. *Eur J Neurosci* 2019;49:307–15.
20 Postuma RB, Iranzo A, Hu M, *et al*. Risk and predictors of dementia and parkinsonism in idiopathic REM sleep behaviour disorder: a multicentre study. *Brain (Bacau)* 2019;142:744–59.
21 Hirsch EC, Hunot S. Neuroinflammation in Parkinson's disease: a target for neuroprotection? *Lancet Neurol* 2009;8:382–97.
22 Stokholm MG, Iranzo A, Østergaard K, *et al*. Assessment of neuroinflammation in patients with idiopathic rapid-eye-movement sleep behaviour disorder: a case-control study. *Lancet Neurol* 2017;16:789–96.
23 Stokholm MG, Iranzo A, Østergaard K, *et al*. Extrastriatal monoaminergic dysfunction and enhanced microglial activation in idiopathic rapid eye movement sleep behaviour disorder. *Neurobiol Dis* 2018;115:9–16.
24 Stær K, Iranzo A, Stokholm MG, *et al*. Cortical cholinergic dysfunction correlates with microglial activation in the substantia innominata in REM sleep behavior disorder. *Parkinsonism Relat Disord* 2020;81:89–93.
25 Stær K, Iranzo A, Stokholm MG, *et al*. Microglial Activation and Progression of Nigrostriatal Dysfunction in Isolated REM Sleep Behavior Disorder. *Mov Disord* 2024;39:1323–8.
26 Rizig M, Bandres-Ciga S, Makarious MB, *et al*. Identification of genetic risk loci and causal insights associated with Parkinson's disease in African and African admixed populations: a genome-wide association study. *Lancet Neurol* 2023;22:1015–25.