Evolving clinical trial protocols in Parkinson's disease: integrating therapeutic innovation and operational excellence

As biomarkers, imaging and digital tools advance, could these innovations redefine how Parkinson's disease trials are designed and conducted?

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Introduction and background on Parkinson's disease

Parkinson's disease (PD) is the second most prevalent neurodegenerative disease, after Alzheimer's disease. PD is characterised by a gradual loss of dopaminergic neurons in the substantia nigra as well as the accumulation of abnormal clumps of alpha-synuclein in the brain. Decreased dopamine levels lead to the cardinal motor symptoms of Parkinson's disease, which include resting tremor, bradykinesia, stiffness of the limbs (cogwheel rigidity) and postural instability.[1]

An estimated 1.1 million people in the US are living with PD. More than ten million people worldwide are estimated to be living with PD.[2] The incidence of PD increases with age, but an estimated 4% of people with PD are diagnosed before age 50; men are 1.5 times more likely to have Parkinson's disease than women.[2] Most PD is sporadic but genetic mutations cause or are associated with PD in 10-15% of all cases.[3] Many patients with PD develop dyskinesias and on/off motor symptoms three to five years in.[4] These motor fluctuations significantly worsen mobility, function and quality of life.

There are multiple approved therapies for the treatment of PD. Most are symptomatic therapies that address the dopamine deficiency caused by loss of substantia nigra neurons. These treatments include various forms of levodopa/carbidopa (oral, subcutaneous, enteral and inhaled forms), dopamine agonists, anticholinergic medications, amantadine, monoamine oxidase B inhibitors, adenosine receptor antagonists and catechol O methyltransferase inhibitors. Deep brain stimulation, with implantation of electrodes into deep brain structures, is used as an adjunct to medications for motor symptom management.[5]

With multiple prior clinical trials of these various therapies, clinical trial methodology and outcome measures have been reasonably well established for drug development in PD. These trials have relied on the clinical diagnosis and staging of PD and clinical outcome measures. The rather static prior methodology of PD clinical trials is now being transformed by scientific advances in PD. Insights into PD pathophysiology have resulted in new biomarker assays, imaging techniques and new investigational drugs. Wearable devices and other digital technologies are also being evaluated for diagnosis and assessment of PD symptoms.

All of these aspects (scientific advances, new techniques, devices and new investigational drugs) are transforming the conduct of PD clinical trials.

PD pathophysiology, biomarkers and staging

The scientific understanding of PD has advanced over the years. While numerous molecular and cellular alterations are theorised to contribute to the neurodegenerative course of PD, such as excitotoxicity, oxidative stress, neuroinflammation and mitochondrial dysfunction, the importance of alpha-synuclein aggregates as a primary pathology is recognised (**Figure 1**). Many of the most promising disease-modifying therapies are targeting alpha-synuclein.[6]

In order to successfully develop a therapy against alpha-synuclein, it is necessary to measure its presence as well change in levels or distribution. This is now facilitated by the recent validation of the alpha-synuclein seed amplification assay (aSyn-SAA) in cerebrospinal fluid (CSF). The assay can detect pathological alpha-synuclein not only in CSF of those with symptomatic PD but also those with preclinical PD. The test is highly sensitive and specific for both sporadic Parkinson's disease with the typical olfactory deficit and those in prodromal groups with REM sleep behaviour disorder or hyposmia.[7]

The validation of the SAA biomarker in those with preclinical PD has enabled the development of a new biological staging system for PD, the neuronal alpha-synuclein disease integrated staging system (NSD-ISS). The framework defines PD by the presence of alpha-synuclein (aSyn) and creates a disease staging system that includes Parkinson's risk, diagnosis and functional impairment. An individual's stage is based on their personal biological profile, including genetic risk factors, CSF aSyn and loss of brain dopamine.[8]

A similar biological framework that incorporates abnormal levels of brain amyloid and tau and cognitive and overall function has been used to stage

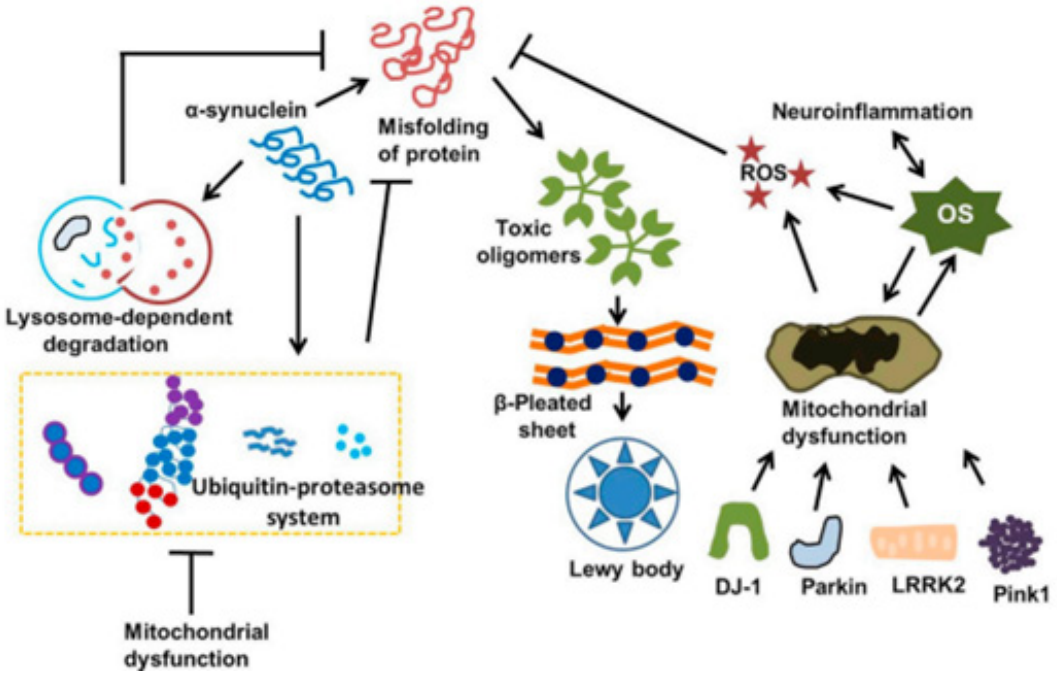

Figure 1: Pathways that alter alpha-synuclein formation include alternations in the ubiquitin-proteasone and lysosomal autophagy pathways. Oxidative stress, changes in mitochondrial function or neuroinflammation may also lead to a build-up of alpha-synuclein. Genetic mutations lead to mitochondrial impairment and indirectly to altered alpha-synuclein balance

Alzheimer's disease patients. This led to successful new AD drug approvals in 2022 and 2023 for therapies that slow cognitive decline.

This new PD framework will help in enrolment of PD patients with early or asymptomatic disease in clinical trials of potential disease-modifying therapies. By creating a more uniform cohort, the assessment of therapeutic effects of new drugs can be better defined.

Gaps remain in the ability to measure change in brain alpha-synuclein. The aSyn-SAA is not quantitative, although effects are underway to be able to measure changes. There is also no imaging yet available for brain alpha-synuclein in PD. A PET ligand was recently found to have good binding in brain areas affected by alpha-synuclein in patients with multiple-system atrophy, however binding was limited in PD. With continued research, it is highly likely that a PET ligand will be available in the near future to measure effects of disease-modifying therapies on alpha-synuclein.[9,10]

Clinical research in PD also continues to focus on symptomatic treatments. An important symptomatic approach is the administration of intraparenchymal stem cell transplants into the putamen or striatum into the brain of those with PD, using neuronal precursors that will produce dopamine. Several companies are actively enrolling PD subjects into these stem cell trials.

In these trials, the ability to quantitatively assess dopaminergic brain function is important, both for validation of initial dopaminergic deficiency and for assessment of response to the cell therapy. The dopamine transporter scan (DaTscan) is typically utilised. The Parkinson's Progression Markers Initiative (PPMI) has published longitudinal data assessing change in dopaminergic degeneration using DaTscan (123I-FP-CIT SPECT) imaging.[11]

Gene therapies are also in development for PD associated with mutations in LRRK2 and GBA. These therapies, respectively, aim to reduce leucine-rich repeat kinase 2 activity or enhance glucocerebrosidase activity. Such trials require the identification of those who possess these rare genes. These studies have additional complexity with the potential need for neurosurgical administration intraparenchymally, careful investigational drug handling and assessments for adverse events of such therapies. Hub and spoke models are often used, with the patient enrolled and assessed at one centre, referred to another centre for drug administration and back to the initial centre for continued evaluations.

Patient identification for clinical trials

Disease-modifying trials in PD need participants with early PD or even asymptomatic subjects with PD. Other symptomatic therapies require PD patients with a specific stage of disease. The need for specific populations means that clinical trials must accurately diagnose PD, accurately stage PD and reliably measure outcomes relevant to assessment of the therapeutic effect. As such, phenotyping of potential PD study participants is vital. Genetic testing, assessment of hyposmia by smell testing using the UPSIT, DaT-scans to measure dopamingeric deficits and lumbar punctures to assay CSF alpha-synuclein are all being employed.

The identification of specific groups of PD patients is being facilitated by initiatives like PD GENEration, which provides free genetic testing, enabling the identification of specific patient populations such as

those with GBA mutations. The Michael J Fox Foundation's Fox Trial Finder connects patients to studies. Parkinson Progression Marker Initiative (PPMI) creates deeply phenotyped patient cohorts, providing valuable data for future clinical trials. As large data sets in PD registries are developed and expanded, artificial intelligence (AI) and machine learning will also be used to assist with precision screening and patient stratification. Online tools and digital marketing strategies may also help recruit PD subjects including from underrepresented groups, by tailoring outreach to specific demographics. Remote identification of those with early PD may be enabled by Smartphone and other AI assessments evaluating speech, writing and speed of movement.[12,13,14] This may improve the ability to screen in a cost-effective manner large numbers of those at risk for PD or those who have early motor symptoms.

Outcome measurement in clinical trials

Clinical outcome assessments are a mainstay of clinical trials in PD. The MDS-Unified Parkinson Disease Rating Scale in earlier phase studies and diaries to measure on-off motor symptoms in more advanced disease are frequent primary outcome measures.[15,16]

Digital technology along with machine learning is being applied to these clinical assessments to improve the accuracy and reliability of measurement of motor and functional changes. In clinical trials, such measures are often included as exploratory outcomes, where the assessment may be benchmarked against the clinical assessments. Several studies show strong correlations between data from smartphone measurement and traditional clinical scale in PD. WATCH-PD is evaluating the use of smartphones to assess motor and cognitive tasks and wearable sensors to evaluate correlations with MDS-UPDRS part three. Longitudinal assessments will inform the value of these digital measures for clinical trials utility. These sensors may also eventually enable at-home assessments and reduce the need for more frequent clinic visits especially in trials of disease-modifying therapies, which are typically longer in duration than those for symptomatic therapies.[17,18,19] The previously mentioned biomarkers are increasingly incorporated to assess longitudinal drug efficacy in PD trials. These include periodic DATscans, alpha-synuclein CSF measures, and other fluid biomarkers for neurotransmitters, inflammation or synaptic function. Alpha-synuclein PET imaging is expected to become an essential aspect of clinical trials for alpha-synuclein therapeutics.

In studies of more advanced PD, the Parkinson motor symptom paper diary is completed every 30 minutes during waking hours for two to four sequential days by patients regarding on-off motor function and dyskinesias. While this information can be collected electronically and entry timing validated, a recent study noted poor correlations between patient and observer especially for dyskinesia. Sensors that can reliably detect and categorise movement such as dyskinesia and freezing of gait are being evaluated and may serve as an adjunct to the diary or one day replace it if greater validity and reliability are established.[20,21]

In summary, new biomarker assays, imaging techniques, wearable devices and other digital technologies are transforming the enrolment and conduct of clinical trials in PD of investigational new drugs that are disease-modifying as well as those that are symptomatic. Continued evolution in trial conduct, methodology and operational complexity is expected over the coming years.

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Dr **Rebecca Evans** is an accomplished medical doctor with extensive experience in Clinical Development and Medical Affairs. With over 18 years of industry experience and prior academic research and patient care experience, her expertise includes neurology, psychiatric and rare disease indications across various modalities and devices. She provides strategic and operational leadership for Linical's Medical and Scientific Operations in Neurology. Prior to joining **Linical**, Rebecca served as the founder of a consulting firm, Qualcosa Neuroscience, and held senior roles as vice president of Clinical Development and Global Clinical lead roles. She earned her MD from the University of Iowa, Iowa, US, and completed her residency training at the University of Minnesota, Minneapolis, US. She completed fellowships in neuromuscular disease and electromyography at Kansas University, Kansas, US, and Neurodegenerative fellowship at Indiana University, Indiana, US.