White paper

Clinical trials

# Recruiting Parkinson's Disease patients for clinical trials

## Addressing the challenges of populating Parkinson's research studies starts with knowing the patient

## Summary

It is estimated that Parkinson's disease (PD) affects nearly 1 million people in the United States and more than 6 million people worldwide.[1] In terms of people affected, this puts it behind Alzheimer's disease[2] (6 million in the U.S.) and on par with multiple sclerosis[3] (1 million). Although there are approved symptomatic treatments for the disease, there is currently no effective disease modifying therapy (DMT) that is FDA-approved. Since the first clinical use of levodopa in 1961,[4] patients and their physicians have focused on treating symptoms, with therapies such as levodopa, dopamine agonists, MAO- and COMT-inhibitors, and amantadine. More recently, however, as researchers come to a better understanding of the mechanisms underlying the disease itself, efforts are underway to address disease progression, including a number of potential therapies (small molecules, antibodies, gene therapies and cell therapies) that are already under study or in development. At the time of this writing, the U.S. National Library of Medicine[5] showed more than 350 PD trials in preparation, enrolling, or underway. These trials test more than 130 new agents currently in Phase I to III development.[6]

In this high-demand area of study, the primary challenge is a familiar one: How to enroll the right patients to the right trials. In the face of longstanding complexities inherent across the field of neurologic disorders, as well as newer obstacles coming out of the COVID-19 pandemic, study sponsors and CROs have their work cut out for them—but success is certainly attainable.

**PARKINSON'S DISEASE**

affects nearly

**1 MILLION PEOPLE**

in the United States

**>6 MILLION PEOPLE**

worldwide

### Staffing and data challenges to trial enrollment

For the most part, recruitment challenges for PD trials are similar to challenges for trials focused on other chronic neurologic indications. Some of these challenges arose during or were exacerbated by the pandemic. For example, patients have been reluctant to visit clinics, and clinics have had to start and stop trials, or reduce their scope, to accommodate pandemic protocols, shutdowns, and staffing or supply shortages—all of which restrict the flow of patients able to participate.

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Staffing can be a particularly challenging issue because these trials typically require expertise in protocol-specific assessments such as the MDS-UPDRS rating scale[7] or other complex disease specific scales. Trial protocols often dictate that the movement disorder specialists, who assess the patients, have a certain amount of experience in these assessment scales—and to that end, online training for PD-specific clinical outcomes are available, including the Movement Disorders Society (MDS) training program for the MDS-UPDRS and some other MDS-owned scales.[8]

Lack of experience can lead to a lack of qualified specialists, which impacts the number of sites and patients who can participate, the amount of data that can be collected, and sometimes even study outcomes (if criteria need to be modified or reduced to accommodate lower standards). A recent study[9] examined inconsistencies and errors in MDS-UPDRS part III (motor assessment) using data from the PPMI initiative. Even where PPMI raters represent excellence in PD research, the percentage of errors (≥1 inconsistency) at baseline and follow-up was 11.8%. This figure likely underestimates occurrences in standard clinical studies where sites use less experienced examiners. This fact underlines the relevance of adequate site selection and exquisite rater training to reduce the error rate in outcome measures.

Though the ability to recruit for a trial is important, the final deliverable is data; and staffing that comes and goes, with lower levels of experience, can have a negative impact on data integrity. This is why it is often a good idea to have a central reviewer to perform an additional data review (possibly even an outside vendor that both provides protocol training and monitors the results throughout the course of the study) to identify potential issues such as "drift" or variability in the rater assessments, or any other shifts in the data that need to be addressed at the site level.

Ongoing centralized monitoring through the process of scientific surveillance can be another useful tool to ensure data integrity. Scientific surveillance looks at the PD protocol measures and findings—efficacy and other endpoints—and applies Bayesian statistics or probability analysis to predict risk, identify outliers, and flag other issues while the study is still ongoing and there is time to react and make adjustments.

This scientific surveillance, developed by our research organization, complements traditional on-site monitoring and goes a step beyond, as the surveillance on blinded data is done while the study is ongoing and allows for on-time corrections. Scientific surveillance is becoming part of centralized monitoring, enhancing data acquisition analysis and triggering corrective actions at a site level, when needed. This procedure improves data quality and significantly reduces the likelihood of meaningful data errors.[10]

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### Locating trial participants

Parkinson's is most often diagnosed in older people (only 4% are diagnosed before age 50)[11] but how the disease manifests is unique to each person. Several factors play a role in disease development including genetic, environmental and lifestyle factors. We also know that the pathological process that leads to the appearance of symptoms starts years before patients experience any impairment. The pre-symptomatic stage characterized by the loss of dopaminergic neurons within the substantia nigra has been the target of new therapeutic interventions aiming to slow or stop the neuropathological process before a large number of neurons are lost. Recent trials have been targeting these early populations and added additional challenges in the search of possible clinical trial populations.

Generally, studies focused on treating the underlying disease will target early-diagnosis patients—in contrast to most of the research done in the last 60 years, which has focused on symptomatic treatment. With Parkinson's, mild and severe disease pose different problems; and as the disease progresses, the patient's needs for care and treatment change as well. Because symptoms generally progress over time, studies focused on symptom management will likely target patients with more progressed disease. For these two distinct types of patients, the treating physicians are different, the patient experience is different, and their needs—including the involvement of caregivers—are different. A lot of factors vary depending on disease progression and study protocol, which is why first and foremost the whole study support matrix must be designed according to who the patient is, what are their needs, and what can be done to facilitate their participation.

Successful recruitment, therefore, begins at the protocol development stage and clearly identifying potential patients. Patient identification should include as much detail as possible, from defining the targeted subgroup (e.g., pre-symptomatic, newly diagnosed, progressed), to describing a plan to access and support those potential patients. For example, general community care neurology practices are typically first to see and treat PD patients, so early diagnosis trials or disease modification trials will do best to work with these practices or with research groups having access to general care neurology practices. Patients with more advanced disease, however, typically require more intervention, care, and support—so studies needing these patients would do better to work through the networks of specialty neurology clinics, universities and academic settings that treat these patients. Patient advocacy groups can be a good resource for promoting a new trial to patients and caregivers as well as identifying potential patients for study sponsors.

## Having a well-defined target patient in mind is prerequisite for all the other steps: engaging with partner sites, enrolling new patients, and keeping those patients engaged for the life of the study.

## Research partners: An important part of the mix

Successful clinical trials rely on a wide range of partners across diverse areas such as protocol development, patient recruitment, data capture, technologies, and more. For example, as with the other aspects of PD just discussed, the assessments/scales used to evaluate patients may vary according to which patient population is targeted as well. As such, study development should also consider factors such as which partner organizations and study sites are licensed to administer any necessary scales, and which vendors are best equipped to deploy them.

Likewise, there are a variety of ways to capture data (electronic data collection, imaging, etc.) and protocol design should also consider those needs. Whether or not the broader systems and overall study approach is similar to clinical trials for other neurological disorders, the specifics are unique to Parkinson's, and vendors and study sites must display therapeutic expertise and experience with scales and other disease assessments that are specific to PD. For example, MS and PD studies might both use MRI imaging, but they utilize different sequences and image analysis protocols. Thus, vendors need to be expert not just in MRI, but in how it applies to this specific disease. The same applies for the use of technologies like DaTscan imaging or PET scans.

It is typical to deploy multiple vendors/technologies on a study, and each of them will affect how data will be collected and fed into the study. There are vendors that specialize in patient recruitment, data collection, imaging, analysis, and more; and each vendor needs to be vetted at the outset and closely managed throughout the duration—including for data integration, cleaning, and analysis. Planning and management of the entire vendor process is critical to a successful study.

While it is clearly beneficial to develop a study protocol to include targeted and focused inclusion/exclusion criteria that will help to identify the ideal participant, it is also important to not be so specific as to exclude all the real-world patients. Likewise, attention must also be given to appropriate screening protocols. (Often, these screenings are from yet another vendor in the mix.) Screening that is too strict can lead to a site failing to enroll enough participants, leading to site exhaustion and disengagement in the study. However, screening that is too loose can increase subject variability and jeopardize statistical analysis and overall data quality. Well-defined pre-screening and screening built into the protocol can be a real time-saver (and cost-saver), as well as an efficient way to identify those participants worthy of more hands-on, in-depth screening.

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In addition to vendors, sites are another important part of the study mix, and here too sponsors are advised to consider multiple factors at the protocol planning stage. While each site has its own database of patients from which to recruit participants, these typically need to be supplemented. There are a variety of strategies available: general advertising; directly contacting neurologists or establishing networks with community-based neurologists; working with patient advocacy groups such as the Michael J. Fox Foundation[12] (with their popular Fox Trial Finder[13]); and engaging recruitment vendors that, among other things, produce literature and work with support groups and local community organizations to get the word out, as well as doing social media outreach and advertising.

By considering the above factors at the planning stage and defining outreach solutions as part of the protocol, sponsors pre-empt any reluctance on the site's part while making it as easy as possible to cast a wider net than usual and to include patients from outside their standard database. As the study progresses, each of these factors will also need to be reviewed, revised, and updated throughout the study to support an ever-changing landscape.

## It's all about reducing patient burden

As with clinical trials for other diseases, PD patient recruitment and retention require a multi-tiered approach, customized to each trial. Addressing the challenges of populating—and maintaining—a meaningful trial starts at the protocol planning stage. This involves not only identifying the optimal patient, but also considering how to retain those patients for the life of the study. For this reason it is important to consider patient burden during protocol development and to limit the number of clinical outcomes and scales to a reasonable number. Input to the protocol by experts such as key opinion leaders or patient advocacy groups can help determine which assessments are able to be done during a study visit without overwhelming or exhausting the patient. Patient burden is affected by such factors as frequency and length of visits (how those visits impact working patients or caregivers, for example) and can be eased through programs like concierge services to help with patient and caregiver transportation, stipends, reimbursement for ancillary expenses, and so on. Overly burdensome trials will be viewed as such, making it difficult for them to recruit patients, but even those that initially do not appear onerous can become burdensome over time and suffer high attrition.

## It is important to always have patient burden top-of-mind during protocol development.

As discussed previously, poor data integrity is the largest threat to creating meaningful study outcomes, and one of the biggest factors in poor data is missing data. A study that cannot retain its patients, or even keep them consistently involved, throughout the life of the study risks diluting the data assessments.

Today's Parkinson's patients are generally able to treat their symptoms and to maintain an active lifestyle, e.g., staying employed longer or acting as caregiver to grandchildren, etc. These patients have full and busy lives, making frequent, long or inconvenient office visits—and the associated transportation—a real hindrance to trial participation. During protocol design, care should be taken to identify and include only what is necessary to ascertain the effectiveness of the drug as pertains to the primary and main secondary endpoints. Likewise, depending on the

stage of disease progression under study, consideration must be given to what level (duration, intensity, etc.) of testing the patient will physically or mentally tolerate. Very long visits that enchain a large number of scales or assessments can exhaust the patient, and the value of the data obtained from a tired, elderly subject is to be challenged.

Moreover, sponsors and academicians need to consider that up to 50% of all academic clinical trials and data are never published[14] (in industry sponsored trials the percentage may be higher) and within the published papers a significant part of the "exploratory outcomes" are not included in the publications and many times have little scientific use, although they increased the patient burden in most cases.

## Where a number of exploratory outcomes must be included, the sponsor should consider dividing them among participants, so each patient is only involved in one half or one third of the total.

Patients become frustrated when a study protocol is too complicated or the assessments are too invasive, overly repetitive, fatiguing, or otherwise unpleasant. Yet all of these factors can be addressed with a patient-centric approach that takes a clear-eyed view of the burden on the patient and continually seeks to mitigate that burden. This starts at the protocol stage with identifying the study's primary and secondary objectives, then reducing as much as possible any other exploratory outcomes. Where a number of exploratory outcomes must be included, the sponsor should consider dividing them among participants, so each patient is only involved in one half or one third of the total.

Patient retention is critical to generating meaningful outcomes and requires a lot of consideration during protocol development. Aside from when unpleasant side effects cause a patient to drop out, the overall experience can largely be controlled (as with the previously mentioned concierge services, for example).

Across the life of the study, the sponsor must work closely with the sites to streamline visits so they are as efficient as possible and to minimize the number of times the patient has to come in while still providing all the necessary data. This includes assessing all the different vendors and systems the patient has to interact with to ensure their smooth interoperation during data collection.

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On the whole, Parkinson's patients are altruistic participants that know any potential outcomes are going to benefit future generations and may not have much impact on the course of their own disease. Nevertheless, every effort should be made to make their participation as easy and pleasant as possible. One easy but meaningful way to ensure the patient feels acknowledged and that their participation is valued is to simply keep them abreast of study results, throughout the study as well as after patient participation is completed. Likewise, informal lectures or updates on the disease and the aim of the study, including mechanism of action of the investigational product, may engage patients in the science they are supporting.

These small steps could positively impact future participation in subsequent trials or might promote positive feedback to future participants of other trials, but beyond that it is simply the right thing to do.

## Decentralized Clinical Trials

When it comes to easing patient burden, decentralized clinical trials (DCTs) have a lot to offer as well. DCTs enable efficiencies through technological solutions such as telemedicine, remote monitoring, direct-to-patient shipments, wearable devices, and more. Decentralized trials present opportunities to emphasize convenience, safety, and flexibility while continuing to pursue quality data and valuable research.

For example, home health visits are useful in that they can broaden a site's reach beyond the local population, reduce patient burden, and present a much more palatable option for frequent participation. Where trials are understaffed onsite, televisits can also be useful in spreading the workload to offsite staff or by increasing staff flexibility.

While virtual visits, eConsent, remote data capture, and digital diaries are all well-documented DCT practices that can play a role in easing patient burden in general, much of the current technology used in decentralized trials is not as applicable to PD as it is to other areas of study.

At present, most of the clinical and biological markers tracked for Parkinson's research are not the same as those tracked by standard wearables. However, in the last years significant advances have occurred in this area (e.g, wearables that measure tremors, gait, dyskinesia, etc.) and technologies that support virtual trials for Parkinson's patients are likely to be a larger factor going forward. Although such new tools are starting to be validated for use in clinical trials, and to a small extent accepted by regulatory agencies, relevant PD data still have to be captured and recorded via face-to-face interaction with the patient using well-known scales (MDS-UPDRS, UDysRS, etc.). Nevertheless, anywhere that virtualization can be used to expand the site's reach or ease the patient burden, it should be strongly considered.

Where DCT tactics and tools are used, additional time should be built into the development stage as well. While reducing patient burden, technological solutions can increase operational complexity and, particularly where they've not been used before, will require time for training and implementation. Likewise, care should be taken beforehand to ensure that multi-vendor devices are integrated with one another and each is producing the expected data. While focused on ways to ease the patient burden, the sponsor also needs to keep site burden in mind as well. In the current market, sites are in high demand and can easily bypass studies that they think will not be worth the trouble. Partnering to conduct the trial and participating as a patient both need to be made as appealing as possible.

## Good trials are good by design

At study outset, during protocol development, keeping patient recruitment top-of-mind will have meaningful impacts on the entire life of the trial. By defining targeted but realistic inclusion/exclusion protocols and being specific about screening criteria, a study improves its chances of successfully recruiting participants. By designing assessments to minimize patient burden across every aspect of the trial, the study helps ensure that patients are willing and eager to participate. Clearly identifying the primary objective(s) and strictly limiting exploratory exercises increases the likelihood that participants won't drop out and will remain fully engaged.

With Parkinson's disease, there are a wide range of patients, from early diagnosis with few symptoms, to long-term patients who treat their symptoms and otherwise carry on as before, to those with advanced symptoms that impact their daily lives and require high levels of caregiving. A successful trial starts with knowing your ideal patient and building a recruitment strategy around that ideal, and it proceeds with taking measures to ease patient participation across every aspect of the study.

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