Clinical Research in Parkinson’s Disease: The Advances, Challenges, and Importance of Rater Training

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April is Parkinson’s disease Awareness Month. Raising awareness and educating the community about Parkinson’s disease is an important way to support the more than 1 million people in the US who have been diagnosed with this disease. Fundraising efforts spearheaded by celebrities, such as Michael J. Fox, as well as by societies and foundations committed to finding treatment for Parkinson’s, contribute to research and to the education of the public about the disease. Community education plays an important role in facilitating early detection of the disease for the 50,000 – 60,000 people who will be diagnosed with Parkinson’s each year.

**What is Parkinson’s Disease?**

Parkinson’s disease is a progressive neurological condition characterized by bradykinesia (slowness of movement), resting tremor, loss of balance, and muscular rigidity. Patients also suffer from a number of other symptoms including depression, anxiety and cognitive impairment. The symptoms are caused by dopamine deficiency resulting from the death of neurons in a specific part of the brain called the substantia nigra.

**How is Parkinson’s Disease Treated?**

Medical management of Parkinson’s disease has focused on correcting the dopamine deficiency to provide control of symptoms for as long as possible while minimizing side effects. Levodopa and carbidopa have been the mainstays of symptomatic management for a number of years. Other medications which have been found to be helpful in early disease include Monoamine oxidase – B inhibitors and dopamine agonists such as ropinirole and pramipexole. Benztropine (as well as other anticholinergic medications) has been found to be helpful as a second line treatment for tremor. Medical management has been found to provide relatively good control of the symptoms of Parkinson’s disease for an average of 4-6 years.

Caregiver burden is marked in those who care for Parkinson’s disease patients. It has been reported that almost half of Parkinson’s disease caregivers have increased symptoms of depression. Caregiver burden is positively associated with the Parkinson’s patient’s increased physical disability and increased incidence of falls, as well as with the neuropsychiatric symptoms which accompany Parkinson’s disease, such as hallucinations, confusion and depression. Caregiver support should not be overlooked, and both clinical and clinical research settings must pay particular attention to providing caregiver support.
Advances in Parkinson’s Disease Research

Further clinical research in Parkinson’s disease is indicated, as patients inevitably exhaust the available treatments for the extremely disabling symptoms of this disease. Pharmaceutical companies continue to seek to develop drugs which provide longer term relief from symptoms and better side effect profiles, and drugs which halt neuronal death, thus stopping disease progression. Clinical research studies are challenging for many reasons including initial drug development challenges, appropriate patient enrollment, difficulties recruiting subjects, and ensuring that the data collected is of the highest quality possible. Ultimately, the acquisition of reliable, high quality data is one of the keys to a successful clinical trial.

Challenges in Rating Parkinson’s Disease Symptoms

In Parkinson’s disease clinical trials, the success of a new compound frequently hinges upon the evaluation of symptom severity at consecutive study visits. When examining a patient during a Unified Parkinson Disease Rating Scale (UPDRS) administration, for example, a clinician must evaluate rigidity in 5 areas of the body- and taking into account his/her experience with Parkinson's patients- assign a score (from 0 to 4) to quantify or describe the degree of rigidity. It is surprising that while the scores at the extremes of such a scale, such as 0=absent/no rigidity and 4=severe, are the easiest to assign correctly, the scores in the middle of the scale, are assigned most frequently. Identifying whether the rigidity is slight or mild/moderate or marked can sometimes be challenging, and very slight differences in symptoms may make a clinician choose a different score. Even more challenging for the clinician, however, is assigning the same score to the same degree of rigidity across many patients. In a clinical trial, data is optimized when all clinicians or raters, at all sites in all countries evaluate the degree of rigidity in the same way at every patient visit for the duration of a clinical trial. Intra and inter-rater reliability is highly dependent on clinician experience with the targeted indication and with study-specific outcome measures.

Certainly, one very important factor in the data optimization equation is clinical experience. A clinician who has examined hundreds of Parkinson’s patients in various stages of illness will be more familiar with different degrees of rigidity (and other signs and symptoms of this disorder) than will a clinician who has seen only 20 patients with the symptoms in question. Intra-rater reliability is more frequently seen in raters who have a great deal of clinical experience with the indication. Consistent ratings are, however, not guaranteed by experience alone. The importance of consistency in the assessment and scoring of a sign or symptom in a clinical trial cannot be overstated since the change in severity from the beginning to the end of the trial may determine the future of the study drug. Raters whose scores are even slightly erratic will introduce error.
Rater Reliability Services include the processes which identify experienced and appropriate raters for a given clinical trial, train those raters on the administration guidelines and scoring conventions of the outcome measures, assess the proficiency of the raters, and monitor rater performance and data consistency for the duration of the clinical trial. These steps not only enhance rater reliability and optimize data quality, but also involve the raters and sites in a team effort to work towards consistency and ultimately, a successful clinical trial.

Considerations for Rater Training

Rater training, most often conducted during investigator meetings, focuses on standardized administration of the outcome measure and on study-specific scoring conventions which will be used in a clinical trial. An optimal rater training program should have the following elements:

- Rater training should ideally be conducted by renowned experts in the field. With their depth of experience, they are able to confer and develop accordance on the assignment of scores to different degrees of rigidity or other symptoms. Didactic presentations are employed to impart the specifics of the study, the study population, the targeted indication, administration techniques and score differentiation.
- Videos which demonstrate administration “do’s” and “don’ts” garner significant attention and interactive commentary from the clinicians and allow those with less experience to learn from the comments of those with more experience. Discussions such as these enhance retention and increase the degree of involvement of the clinician audience.
- Dividing the audience into smaller groups and providing an expert and a patient allows every clinician to examine various degrees of rigidity and tremor. Breakout sessions allow a subject matter expert to correct administration errors, achieve a scoring consensus within the group and impart scoring tips which would aid the study clinician in rating the instrument reliably for the duration of the study.
- Once training is complete, assessment of the learning is recommended to ensure that the clinicians have retained the information which will allow them to assign the same scores to the same degree of severity.
Post-Training Considerations

Despite the use of experienced raters who have received excellent training and the enrollment of appropriate patients, data quality may still suffer as a result of subtle changes that occur in the administration and scoring of the primary endpoints over time. Known as “rater drift,” this phenomenon is, unfortunately, a fact of life in clinical trials. In order to identify rater drift before it threatens data quality, ratings should be monitored for consistency. This allows for timely intervention and for the reinforcement of administrative guidelines and scoring conventions when necessary.

Video monitoring is one way to help the raters recalibrate if they are drifting away from the expected degree of proficiency. This process requires the rater to videotape his/her evaluations of patients and to upload them onto a secure server. The videos are reviewed by the Subject Matter Experts who contact the rater regarding any errors which are identified on the videos. Experts who assess videotaped evaluations often identify scale administration and scoring errors on the videotapes which would have previously gone unaddressed.

A final step in the data optimization process is data monitoring. Inter-scale and inter-visit scoring consistency may be assessed by comparing the scores of outcome measures across visits. Apparent inconsistencies are not uncommon; however contact with the rater is the only way to determine whether there was a psychosocial factor, an environmental cause, a data entry error, or an idiopathic inconsistency.

At ePharmaSolutions, we believe that rater reliability services are most effective if the process is a collaborative one between the sponsor, the rater reliability service partner, and the raters. In our experience, raters are most often expert clinicians who are dedicated to their work. We find that a collaborative team approach is the best way to facilitate the acquisition of high quality data. ePharmaSolutions clinicians work closely with raters to assess why they may have taken a different approach to a patient, as well as reasons that specific scores have been assigned. Every score matters and discussions with raters are at the heart of our Rater Training process – after all, the raters are the ones who have examined the patients!

This April, ePharmasolutions extends our heart-felt support to those struggling with Parkinson’s disease, and to their clinicians and caregivers. We also applaud researchers in academia and the biopharmaceutical industry who are working to develop drugs, which will improve the condition of Parkinson’s disease patients, halt the progression of this disease, and at some point in the future, help to prevent it altogether.