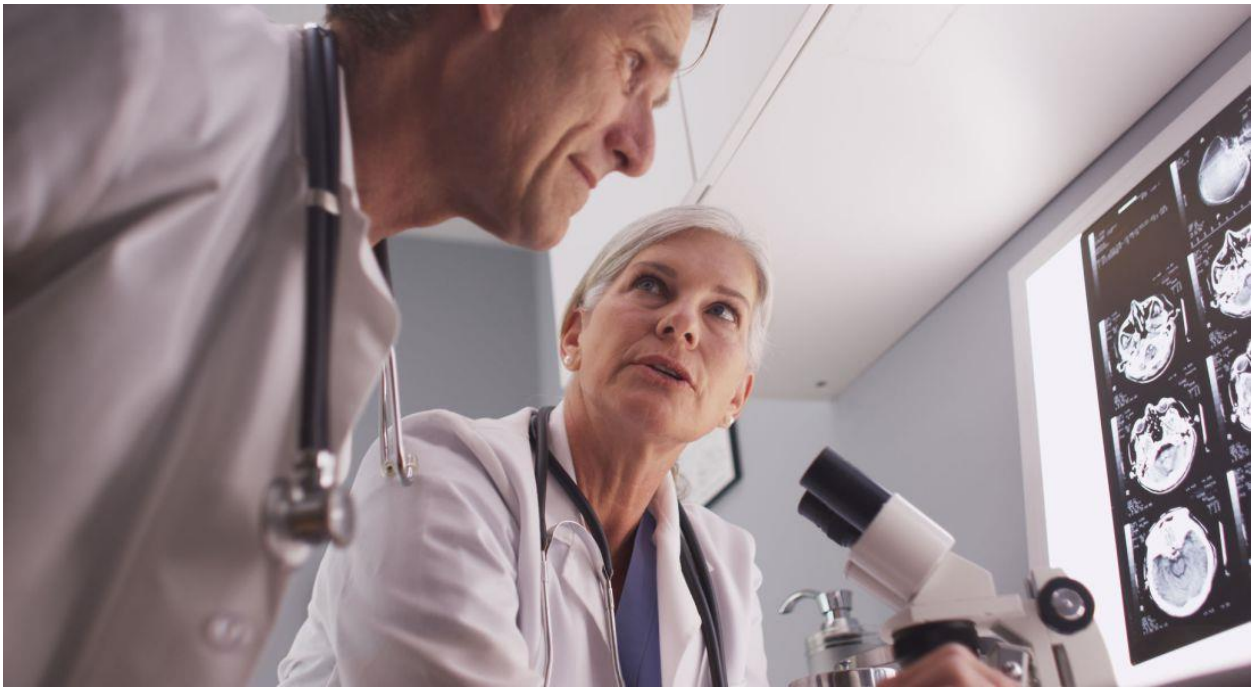

Traditionally hard-to-treat neurological diseases – including Alzheimer's and Parkinson's – which were once considered to be common, are being reclassified as a collection of rare diseases based on genetic markers.

Improving Clinical Trials for Rare Diseases of the CNS

The business of discovering and developing new drugs has historically focused on finding therapies which will benefit the largest patient population. But as our understanding of the genetic basis of disease has matured in recent years, the focus has shifted to using a precision medicine approach to treat patients using personalized therapies designed to work best in the unique environment of an individual.

While oncology is the quintessential example of an area that has – and continues to be – highly influenced by precision medicine, drug development in the fields of neurological and psychiatric disease is increasingly trending the same way. Traditionally hard-to-treat neurological diseases – including Alzheimer's and Parkinson's – which were once considered to be common, are being reclassified as a collection of rare diseases based on genetic markers.

"In the neurology clinic, we see a large number of rare disease, and many of them are genetic in nature," says Dr. James Vornov, Vice President of Medical Affairs in Neurology at Medpace, a clinical contract research organization. "One of the interesting things though, is that as we've understood the genetic underpinnings of these genetic diseases, we haven't always gotten the kind of insight into pathophysiology that we might like."

To learn more about rare disease disorders and CNS drug development, watch this on-demand webinar from Medpace.

From Common to Rare Disease Classification

In the 1980s, a single mutation in the gene that encodes a copper transport protein was found to be the genetic basis of Wilson's disease, a condition characterized by abnormal copper metabolism. According to Vornov, while uncovering the genetic mutations behind some diseases has done much to explain the etiology of the condition, the same often can't be said for neurological and psychiatric diseases.

For example, the occurrence of CAG repeats has been implicated in the development of the rare neurological disorder Huntington's disease, but how this genetic aberration leads to neurodegeneration in adults is still unknown. Similarly, the identification of genetic risk factors for Alzheimer's disease has led to the division of individuals into smaller, more specific categories, despite the lack of understanding regarding how the gene mutations contribute to the accumulation of amyloid in the brain.

"Alzheimer's disease diagnosis is generally made clinically, not until late stages, and you can't make a clinical diagnosis in the prodromal early stages," says Vornov. "But because we have biomarkers, CSF and PET, we've started redefining the broad category of Alzheimer's disease really to be amyloid disease: patients who are accumulating amyloid in their brains.

"And as we've now delved into being able to find the pathology, early on we find risk factors like ApoE4, APP and presenilin, which are in the amyloid pathway, and these allow us to identify patients or individuals who have no sign of disease, but are very likely to, when scanned and looked at for biomarkers, have the beginnings of amyloid disease, thus letting them be treated beforehand with primary prevention of amyloid accumulation."

Common genetic risk factors among heritable diseases once thought to be completely distinct conditions are also causing genetic diseases to be reclassified along a spectrum of related disorders. Vornov gives the example of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) which, until recently, were considered to be two different diseases. However, researchers identified that the highly-conserved TDP-43 gene implicated in the neuronal accumulation of tau protein in some patients with FTD, could also explain some of the dementia-like symptoms noted in ALS patients. Now, researchers recognize that both ALS and FTD are on the same spectrum of TDP-43 diseases.

Similarly, genome-wide sequencing and exome sequencing have both identified a number of genes associated with sporadic and familial forms of Parkinson's disease. These genetic variants have been found in the α-synuclein gene, and the PARK genes, among others, and have led to understanding that the clinical syndrome of Parkinson's disease can be caused as the result of many pathways, some of which are related to other neurological disorders. For example, patients with the metabolic disorder known as Gaucher disease have a higher incidence of Parkinson's due to a shared genetic variant.

Understanding the etiology of these diseases in a new way is leading physicians and trialists to take a different approach when it comes to treatment.

“This has been called the ‘precision medicine approach’ where we start off clearly with syndrome, localization, behavior, signs and symptoms, but then we subgroup the patients based on their genetic diagnosis, what metabolic pathways are involved, what cells are being killed or not functioning well,” said Vornov. “And, of course, in some patient groups there may be other genetic factors that are either worsening speeding the disease or actually may be protecting some patients from the disease. Based on the subgroup, we would then choose a targeted therapy that would prevent that particular pathology, or reverse it, or mitigate the pathology, specifically based on what pathology was driving the disease in a particular patient population.”

This approach will be familiar to those working to develop orphan drugs for rare diseases. Since many rare diseases are caused by a distinct genetic mutation, the practise of categorizing patients based on their genetics in clinical trials has helped to lead to the development, and subsequent approval, of therapies capable of treating the disease.

The regulatory environment has also changed in recent years in an effort to encourage R&D on rare disease drugs which may only benefit a small patient population. The growth in the number of orphan drug designations handed out by the FDA has significantly contributed to the rise in orphan drug approvals; in 2016, 41 percent of all drugs approved by the regulator had rare disease indications.

But while enzyme replacement therapies for inborne errors of metabolism have been some of the most successful drugs in the rare disease space, they are not without their limitations. First, these therapies must be delivered on a regular basis – usually weekly or monthly – and can cost upwards of $100,000 per year of treatment. Since this treatment is not curative, most patients require the therapy to replace a missing or non-functional enzyme for the remainder of their lives, representing a significant financial burden.

Further, since these treatments are largely delivered via intravenous injection, they have little impact on the central nervous system (CNS). This is just one of the many hurdles faced by developers of orphan drugs, and as more neurological disorders begin to be understood in the context of a rare disease, companies working on CNS drugs will face the same obstacles.

Vornov explains that researchers working in the neurological disease space will see “the same kind of challenges that you see in rare and orphan diseases of finding these patients, identifying them, enrolling them and then keeping them in what can be very small trials spread geographically.”

“One of the things that we’ve learned from rare diseases is that often when you target the actual cause of disease, the effect size in the trial is larger and smaller trials are possible.”

Strategies for Enrolling Patients in Rare Disease Studies

The whole process of enrolling participants in rare disease clinical trials begins with identifying the right patients for the right treatment. According to Dr. Richard Scheyer, Vice President of Medical Affairs in Neurology and Pharmacology for Medpace, when it comes to diagnosing patients, clinicians can fall into one of two categories: lumpers or splitters. Lumpers prefer to group all patients with similar clinical presentation of a disease together, while splitters believe that the subtle differences in symptoms experienced by each patient are important to consider when categorizing them.

“We’ve known for a long time that treatment may work in only a subset of patients but only recently have we begun to understand why, allowing us to move from trial and error to mechanism-based treatment selection and precision therapies,” says Scheyer. “This molecular and genetic understanding may be shifting the balance in favour of the splitters.”

While reclassifying common CNS diseases into genetic subgroups can have its benefits, it can also limit the types of patients eligible to participate in a clinical trial, and necessitates a modified study design. According to Michelle Petersen, Senior Associate Director of Clinical Trial Management for Medpace, there are a few things sponsors and sites should keep in mind to help maximize patient enrollment and retention in rare disease studies.

The first strategy is something that’s being adopted by clinicians working across all disease areas: the idea of patient-centricity. Petersen recommends that the patients’ needs and wants be taken into consideration early on in the process – preferably before the study protocol has been finalized.

“To address the concern of patient-centricity, it’s more than just a buzzword. You need to understand what’s important to your patient and how study burden can be reduced,” says Petersen. “You want to make sure that your design is appropriate with endpoints to make sure that your patients are going to be happy with the treatment that you’re providing.”

The risk/benefit profile should inform all patient-facing aspects of the trial. A well-written consent form can ensure that patients understand what it means to participate in a clinical trial, and what the potential benefits are for them. In pediatric trials in particular, Petersen highlights the utility of video and illustration-based consent aids in removing some of the fear and uncertainty surrounding trial participation and the procedures patients will undergo.

Reducing patients’ burden is another key to being patient-centric which can benefit the study investigators in the form of improved patient retention. Minimizing the stress and inconvenience of site visits is paramount.

If the study design and safety profile allow, the study medication can be delivered directly to the patient’s residence, and homecare nurses can perform minimally-invasive tests. If the safety profile of the drug is not conducive to home administration, site visits can be made more convenient by maximizing the window of time open to patient visits. This ensures patients spend less time away from home, work and family.

Transportation can be offered to patients who live far away from the study site and would otherwise be unable to participate in the trial. Depending on the situation, providing accommodation for certain patients as well as their caregivers could go a long way to breaking down barriers to engaging in the trial.

In a patient-centric trial, study staff can also take this idea one step further by supporting patients' health and wellbeing outside of the study environment.

"Related to comfort, often in rare disease, patients feel isolated," says Petersen. "You can really help them by providing them access to networking within their own groups as well as counseling, and even transport to advocacy meetings to make sure that they're connected within their community."

Connecting with a patient's transferring physician during the enrollment process can also help build confidence in both the mind of the doctor and the patient when it comes to participating in a rare disease clinical trial. According to Petersen, facilitating a discussion between the transferring physician and the new treating physician about patient social situations, travel distance and patient disposition is important, and physicians are often willing to complete this step free-of-charge in an effort to improve a patient's treatment options.

In addition to fully engaging patients once they've been enrolled in the study, Petersen suggests establishing referral networks to attract additional patients to your study. Since rare disease patients are often geographically spread out, being able to rely on an established referral network can help bridge this gap and increase enrollment in your rare disease trial.

If registry data is available, this can help identify where rare disease patients are being treated, and which physicians specialize in serving this population. Patient advocacy groups can also be a great resource as they can identify pockets of patients who may otherwise be overlooked.

After these referral networks have been established, it's important to make sure that they're being used optimally to attract the right patients to a rare disease clinical trial. Petersen says that sponsor-approved messaging should be communicated to local staff who can reach out to investigators via phone, email, newsletters and in-person visits.

Using the strategies of patient-centricity and referral networks, Petersen says that the Medpace team was able to double patient enrollment numbers in a Phase III Duchenne muscular dystrophy subtype study. Genetic testing programs also helped them improve patient awareness of the trial by acting as a pre-screening program prior to enrollment.

"Training the local associates to connect with that local staff really does make sure that cultural sensitivities are paid attention to and that personal relationship is built," say Petersen. "In this particular case, we were able to support cross-border travel for about ten countries for patients traveling from one country to another to supplement our recruitment."

Targeting the CNS

Once the right patients have been enrolled in the trial, the challenge becomes measuring the efficacy of the experimental treatment and determining whether it's producing the desired effect. However, invasive drug delivery methods, such as IV injection, can complicate this measurement and establishing whether the therapy actually reaches the target tissue can be difficult.

"Unfortunately, for treatments intended to slow disease progression, clinical confirmation of efficacy may take months or even years and confirming the delivery of our treatment and impact on biological pathways assumes particular importance," says Scheyer.

For diseases that affect the CNS, it can be hard to collect tissue samples capable of confirming diagnosis, measuring disease progression or even monitoring the effectiveness of a specific treatment. For example, a tissue biopsy is often used to study samples in oncology, but clinicians are often unable to take a biopsy of the brain or spinal cord, except in the case of a post-mortem.

Imaging, such as molecular PET, has been used to confirm diagnosis of diseases like Alzheimer's and Parkinson's, but target limitations and concerns over radiation exposure have limited its use. Scheyer explains that cerebrospinal fluid (CSF) has been a more useful way to detect disease markers, but because of its relatively invasive nature, a few considerations must be taken into account before it's used during a trial.

"When introducing CSF collection in a clinical trial, it's important to work with the site to pre-empt any patient or family fear or resistance, or even investigator fear or resistance," says Scheyer. He stresses that investigators need "to use appropriate needles to minimize headache and to attend to factors that may impact the analyses, such as circadian fluctuation in various markers."

Drug development for neurological diseases faces another hurdle: how to get therapies past the blood-brain barrier. While protein, antibody, gene and cell therapies could be effective ways to treat diseases affecting the CNS, even small molecule drugs are often blocked from entering the brain by this barrier, representing a significant challenge in drug delivery.

The blood-brain barrier challenge has prompted some drug developers to seek out other ways of getting their therapeutic to its target. Neurosurgical delivery of therapeutics directly into the brain, and injection into the CNS via the CSF have both been tested, however these methods also have their limitations.

For example, Oxford Biomedica's ProSavin is a gene therapy designed to increase dopamine production in the brains of patients with Parkinson's disease. While the therapy had a favorable safety profile in clinical trials, it was only moderately efficacious.

Some studies have found that therapies being delivered to the brain through the CSF could be promising to localized targets, but the drug often fails to reach deeper tissue. This is the case with nusinersin, an anti-sense oligonucleotide that modifies pre-messenger RNA splicing of the

SMN2 gene, which, in turn, increases production of motor neuron protein in spinal muscular atrophy.

According to Scheyer, molecular modifications could help drugs cross the blood-brain barrier, even when they're delivered intravenously. Designing a drug that's lipid-soluble could help mediate this drug delivery problem, however the effects of active transporter efflux, which can pump drugs back out of the cell, can be hard to overcome.

"Carriers and transporters are also available that can help even macromolecules reach the brain," says Scheyer. "In particular, receptor-mediated and absorptive endocytosis may allow otherwise nonpenetrant therapies to reach the brain."

Finally, Scheyer says that fusion proteins and the use of CNS trophic viruses as vectors are some promising new approaches in this area of drug development. Both tactics have the potential to lower the traditionally large systemic doses necessary to have a measurable effect, with the ability to edit the promoter sequences of viral vectors and increase their target specificity.

"Such therapies hold the potential to modify the genome of the target cells, so instead of requiring a lifetime of administration it's possible to administer just on one occasion," says Scheyer.

But once the drug delivery method has been optimized, the question becomes, "did it reach the CNS?" Utilizing tools to measure the impact and effectiveness of experimental CNS drugs is also trickier than in other disease areas.

Again, PET labelling can help confirm that the drug has entered the brain and even bound to its target receptor, so this technique is commonly used for psychiatric therapies. While it's possible for catheters within the brain to sample extracellular fluid, this type of assay is rarely done in human patients because it is highly invasive.

While sampling the CSF might not give an accurate estimate of drug concentrations within the brain, it can help assess the level of target engagement for a given therapy. However, the invasive nature of lumbar punctures prevents frequent sampling of CSF.

Perhaps the most important variable to consider is whether the treatment actually improved patient outcomes.

"Indications with very few available patients need the best possible study designs," says Scheyer. "This is true for orphan diseases, and again true when subsets of common diseases become orphan. Clinical evaluation of the patient is critical."

He stresses that when it comes to assessing outcomes in neurological clinical trials, careful rater training and certification are crucial. Patient-reported outcomes also play a key role in this type of trial, particularly if blinding study staff is difficult, as is the case with neurosurgical treatments.

These patient-reported outcomes are increasingly being facilitated by personal devices and the ever-present technology that patients use in their everyday lives.

“Bring-your-own-device has become increasingly common in clinical trials,” says Scheyer. “It alleviates some of the burden of trying to provide devices across large scale trials and increases the patient acceptance of not having to carry multiple devices around.”

Home monitoring devices – including wearable sensors and home video systems – can act as an objective supplement to the patient’s own responses.

Ultimately, the goal of these rare disease clinical trials is to gather the most data from the often small number of enrolled participants, while ensuring that the burden on patients and sites is minimized. Despite the challenges inherent to rare disease studies, categorizing patients into smaller subsets may aid in the development of the most efficacious therapies.

Dr. James Vornov, Dr. Richard Scheyer and Michelle Petersen share more insights into applying a precision medicine approach to CNS drug development for rare diseases in this on-demand webinar**.**