Neurodegenerative disorders present some of the biggest challenges in planning and conducting clinical drug trials. Diagnosis is challenging, given the often-delayed onset and diversity of symptoms. Operational challenges associated with clinical trial development complicate things even further. Identifying strategies to proactively address or mitigate these challenges can help to ensure a successful trial.
Introduction
Since the first drugs for neurodegenerative diseases (NDDs) were approved in the 1990s, an increasing number of disease-modifying therapies have been approved for multiple sclerosis (MS) and several symptomatic therapies have been approved for Alzheimer’s disease (AD). However, despite extensive research, none of these available treatments demonstrate the ability to halt neurodegeneration. Hence, developing drugs that can stop clinical progression remains the biggest challenge in NDD.

Recent advances in our understanding of the genetic, molecular, and cellular basis of neurodegeneration make this an exciting time for NDD research. As our understanding of NDD has increased, so has our understanding of how to conduct clinical trials to study them, including design, assessments, and biomarker use. For example, we know that patient profiling and adjudication of endpoints or adverse events of special interest can have a significant impact on drug development.

In this white paper, we explore the complexity of neurodegeneration and the operational challenges inherent in NDD studies. We also introduce strategies for mitigating these challenges to ensure a successful trial.

Complexity of neurodegenerative diseases
Neurodegenerative diseases are complex, both genetically and etiologically. Disease measurement can be vastly different based on biological variation, which presents a significant challenge to therapeutic development.
Developing representative phenotypes

Biological variability, clinical and radiological variability, and pathology and genetic heterogeneity all need to be considered when defining an NDD phenotype for a clinical trial. The same proteinopathy can present as different, distinct phenotypes and different proteinopathies can present with overlapping phenotypes. To further complicate matters, combination proteinopathies are a frequent occurrence.

We still do not know what triggers or accelerates neurodegeneration and spread of the disease, even in genetic NDDs. What we do know is that the pathobiology of NDD results in the distribution of different proteins in cells and subcellular structures, and we need to understand the overlap in the pathogenesis of different disorders to translate investigative compounds into effective therapies.

Given this variability, having biomarkers to predict prognosis and progression beginning in preclinical development would be ideal. Unfortunately, there are few preclinical animal models that translate to human disease in NDD.

To reach an endpoint with a targeted therapy, a clinical trial needs to separate among phenotypes and consider the distribution of pathology. In defining a clinical phenotype, sponsors can use biochemical or radiological means to separate subtypes. They should also consider the genetic background of the disease, while taking into account the influence of genetic polymorphisms, the environment (e.g., in multiple sclerosis), and age (e.g., in Alzheimer’s disease).

Translating therapies into the clinic

Sponsors of investigative NDD compounds should consider the following:

- **Delivery and device.** Identify a mode of delivery (inhaled, intrathecal, intravenous, oral, sublingual, subcutaneous, intramuscular, transdermal) that is appropriate for the therapeutic area.
- **Rare disease strategy.** Consider whether evaluating the investigative compound in a rare disease will provide proof-of-concept for a larger therapeutic area.
- **Value of preclinical models.** Evaluate the ability of a preclinical model to translate to a human study.
- **Regulatory hurdles.** Understand regulatory requirements across the development life cycle in the populations and regions where the therapeutic would be studied and marketed.
- **Competitive market analysis.** Understand the competitive space three to six years in the future, if possible.
- **Payer space and healthcare system requirements.** Estimate product value and reimbursement and understand how the therapeutic will be incorporated into patient pathways.
- **Patient-focused drug development.** Remember that regulatory agencies are increasingly emphasizing patient-focused drug development that considers quality of life and encourages patient engagement.
- **Advocacy involvement.** Allow advocacy groups to participate in the process.
- **Patient recruitment.** Consider strategies for difficult-to-enroll spaces such as MS.
- **Review of previous studies.** Perform a publication review to understand why previous products may have failed.
Importance of molecular pathogenesis and classification

In most cases, clinical symptoms overlap during the course of the disease. Thus, clinical classification is helpful for focusing on the early symptoms. Major clinical symptoms seem to be determined by the anatomical region showing neuronal dysfunction or loss, but do not necessarily reflect the underlying molecular changes that might be seen on imaging studies.

There are several, often inter-related pathways which can contribute to neuronal damage and an understanding of which pathways predominate in different conditions or clinical phenotypes is necessary for developing clinically meaningful therapeutics. For example, a therapy that targets neuroinflammation may be useful in the early stages of MS, when the disease is highly inflammatory, but ineffective in progressive MS where neurodegeneration continues despite the absence of inflammation. This underpins the importance of molecular classification of NDDs for fine tuning our knowledge of pathogenic pathways and our ability to develop effective targeted therapies.

How heterogeneous phenotypes impact clinical studies

The heterogeneity among NDD patients leads to:

+ Wide intra-patient and inter-patient variability
+ Difficulty in pinpointing exactly when neurodegeneration begins
+ Variability in disease progression and ability to predict progression

Consequently, oversimplification of disease groupings with the aim of developing therapies for as many people as possible has not led to success.

Rather, defining novel clusters (e.g., patient profiles, early disease, or active disease) with the help of an enrollment committee and using a stratified approach and an adaptive design to select the right population and dose based on clinical, neuroimaging, and biochemical data that is continually updated throughout the course of a trial is critical. In fact, molecular signatures are expected to be incorporated into eligibility criteria in the near future.

While this strategy for NDD therapeutic development can be costly, the use of high technology (e.g., imaging and biomarkers), high science (e.g., transcriptomics and proteomics), and enrollment committees to specifically diagnose and define disease activity may be the future of neurodegenerative disease research.

Clinical trial challenges

The evolving landscape in NDD research over these last two decades has impacted current clinical research in this area and provided valuable insight into why so many products fail in preventing disability progression in Phase III trials. When designing a clinical drug development plan, several key factors to consider to help increase the likelihood of delivering conclusive results include:

+ How to define a homogeneous patient population
+ How to predict disease progression
+ Whether or not to use a placebo control
+ How to determine sample size
+ How to select sites
+ How to ensure safety
A potential selection bias exists where patients with either mild or very severe disease may be excluded because there are safe and effective marketed therapies which avoid the higher risk associated with an unknown experimental therapy.

Defining a homogeneous patient population

With the exponential increase in randomized controlled trials (RCTs) for NDD – and, consequently, the number of therapies available on the market – it has become clear that a major reason for failure of products to prevent disability progression is the change in patient phenotype since the first NDD drugs were approved in the 1990s.

In particular, patient populations in recent studies are characterized by lower disease activity level at the time of trial entry than they were in the past. A potential selection bias exists where patients with either mild or very severe disease may be excluded because there are safe and effective marketed therapies which avoid the higher risk associated with an unknown experimental therapy. When patients enter a study with less active disease, it may be more difficult to successfully reach trial endpoints and the likelihood of detecting differences with respect to placebo or a comparator is reduced.

Another change in patient profile as compared to the past is the limited patient pool. For example, the treatment naïve population in MS is shrinking in the EU because the current EU treatment guidelines recommend starting treatment early in the course of the disease. While this has limited the pool of treatment naïve patients, there remain untreated populations, especially in developing countries where access to standard of care (SOC) therapies is limited or poorly reimbursed. This can have a major impact on country and site selection.

Disease heterogeneity is another important factor involved in clinical trial failures as it can lead to difficulties in diagnosing the right patients for a study. First, an NDD patient recruited in a clinical trial may not be representative of the general patient population. In addition, current therapies are targeting early stage disease, which may be challenging to diagnose because these patients have fewer clinical symptoms. The risk of misdiagnosis is real, and misdiagnosed patients have likely entered clinical trials in the past. Consequently, sponsors may want to consider employing a sound eligibility review process, as well as enrichment strategies, to ensure that the right patients are entering a study.

Finally, there is a lack of reliable clinical endpoints for predicting disease progression. As a result, sponsors are increasingly including biomarker assessments as primary endpoints in Phase II trials, and as supporting endpoints in the Phase III trials. For example, MRI lesion activity is often used as subject selection in current MS trial protocols; however, sponsors should keep in mind that MRI parameters correlate poorly with clinical outcomes in individual patients.

Predicting disease progression

Many disease-modifying designs have been tested with the aim of predicting disease progression, without any success to date.

In a recent systematic review, McGhee and colleagues compared 128 RCTs in Parkinson’s disease (PD) and Alzheimer’s disease (AD) from 1980 to 2015. These trials employed a variety of design strategies (e.g., wash-in and wash-out analyses, delayed-start, and long-term follow-up) either alone, in combination, or in conjunction with a biomarker, to try to demonstrate the disease-modifying properties of therapeutic agents over any symptomatic effect. However, the authors found that none of the studies reviewed definitively demonstrated disease modification.

The authors concluded that the best clinical trial design available to demonstrate disease modification is a well-designed, long-term follow-up study. In a long-term follow-up study, disease modification is inferred from sustained divergence in outcome measure, including time-to-event outcomes, between treatment arms over the study period. While long-term follow-up studies may be the best design to show disease modification, these trials are time consuming and expensive. Cost can be mitigated by choosing outcomes that can be selected from routine data (e.g., mortality data from national death registries). The length...
of follow-up will vary, but will ultimately depend on finding the balance between waiting long enough for disease modification to become apparent without unacceptably high rates of attrition.

Future long-term follow-up studies must not simply compare outcome measures between groups at the end of the study, but also provide clear evidence of sustained divergence in those outcome measures throughout the trial. The latter requires clinical assessments to be conducted at several time points during the trial to enable a meaningful slope analysis.

Using a placebo control
Given the increase in effective NDD therapies over the past two decades, the use of placebo-controlled trials has become more difficult from both an ethical and practical perspective. Placebo use always requires mitigation and is subject to close scrutiny from regulating bodies. Even though placebo is still the comparator of choice for regulators in AD and PD, its use could significantly impact site selection and enrollment rate as there is tremendous competition for trials in NDD, giving both sites and patients a variety of options for clinical trial participation.

Placebo use may also be ethical for relapsing-remitting MS (RRMS) patients who have failed other therapies. But, with the growing success of disease-modifying therapies (DMTs) for early stage RRMS, the use of placebo in controlled trials of new DMTs for RRMS is subject to ongoing debate and has been the subject of repeated policy statements and recommendations by international committees since 2000.

As further data have accumulated demonstrating a reduction in long-term morbidity and mortality with early initiation of DMTs, a growing consensus has emerged that further inclusion of placebo arms in clinical trials of novel RRMS therapies is no longer ethical.2

Determining sample size
Modern trials require large size samples and long durations, which are challenging given the limited patient population and high competition for NDD trials. Current DMTs for MS were approved based on demonstrated benefit on clinical relapses and, in some cases, disability accrual as measured by the Expanded Disability Status Score (EDSS). Clinical endpoints recommended by EMA Guidelines may not be sensitive enough to demonstrate additional efficacy, as intra- and inter-patient relapse rate and disability are evolving.

As a result, MS trials today require a sample size of at least several hundred patients and a study duration of two to three years to ensure statistical power with these clinical endpoints. For AD, trials may need to be as long as five years. Using an existing DMT as a comparator with the current clinical endpoints would require even larger sample sizes and longer durations to reach statistical power.3

Unfortunately, historical data for sample size estimation and re-estimation has limited utility due to changes in patient profiles and advances in imaging technology. There are now different diagnostic criteria and clinical endpoints that render past studies irrelevant for informing future studies, and it is clear that new and creative solutions are necessary.

Selecting sites
The NDD clinical trial arena is extremely congested, giving patients and clinicians a wide selection of trials and therapies to choose from. This variety has impacted both enrollment and drop-out rates. To be competitive, sponsors must carefully choose their clinical sites and will likely need to recruit across several continents. In many cases, sponsors will need to recruit in non-traditional countries, giving rise to logistical and operational challenges in generating consistent, reliable data.
Considerations for choosing a clinical site include:
+ Treatment guidelines and SOC in that country or region
+ Access and reimbursement of already-approved therapies
+ Algorithms for switching therapies in the SOC pathway
+ Incidence of the disease of interest in that country or region
+ Acceptability of placebo

**Ensuring safety**

There is an emerging degree of conservatism by many regulatory agencies requiring stringent safety measures to be included in clinical protocols. Thus, sponsors may need to implement additional Data Safety Monitoring Committee (DSMCs) or Independent Adjudication Committees (IACs), and implementation of these committees needs to be factored into the start-up timelines.

Regulators may also ask for additional safety data that could delay the market approval or additional post-marketing safety studies which could have significant cost impact on the clinical development plan of the investigational NDD drug.

**Strategies for successful conduct of neurodegenerative disease trials**

The design and delivery of NDD programs pose significant challenges over traditional clinical trial programs, in part due to significant inter- and intra-patient variability in terms of disease presentation, progression, and severity. As such, historical methodologies need to be replaced with new strategies designed to handle the evolution in patient profiles.

New design strategies now focus on subject enrichment, adaptive designs, and comorbidity analyses. In addition, it is important to consider the operational aspects of delivering these uniquely-designed clinical trials. Special attention should be paid to whether to employ placebo or active-comparator clinical trials. Site selection and qualification require more investigation as trials become even more specialized in terms of disease diagnosis, required equipment, endpoint assessment, and overall study complexity.

**Subject enrichment using biomarkers**

According to the FDA, subject enrichment in clinical trials is defined as the prospective use of any patient characteristic, whether it be demographic, pathophysiologic, historical, or genetic, to select a study population in which detection of a drug effect is more likely than it would be in an unselected population. Enrichment occurs in virtually every clinical trial and is intended to increase the power of the study by:
+ Decreasing heterogeneity
+ Identifying patients with appropriate disease severity
+ Finding those patients who are more likely to respond to treatment

Subject enrichment strategies in NDD now focus on the use of biomarkers (e.g., MRI, PET, CSF, blood, EEG) for disease diagnosis, endpoint assessment, and ultimately identification of a drug response.

The use of MRI in MS trials is well documented and goes far beyond the diagnostic process. MRI techniques can be used as regular monitoring to measure MS disease progression. MRI can also be used to measure lesion burden, thus providing useful information for the prediction of long-term disability. With the introduction of a new generation of immunomodulatory and/or immunosuppressive drugs for the treatment of MS, MRI also makes an important contribution to the monitoring of treatment, and can be used to determine baseline tissue damage and detect subsequent repair. This use of MRI as a biomarker can help predict treatment response and assess the efficacy and safety of new therapies.
In amyotrophic lateral sclerosis (ALS), technological advancements have led to the discovery of candidate biomarkers in biofluids, such as CSF. With its approximation to the brain and spinal cord regions, CSF is an ideal medium for biomarker discovery. A number of biomarkers found in CSF, including matrix metalloproteinases (MMPs) and neurofilaments, have shown the potential to serve as biomarkers for monitoring disease progression and may even provide insight into disease pathogenesis, though their application to clinical trials requires further work.

PET imaging is used to detect amyloid plaque in the brain and its relation to AD diagnosis and disease progression, and has been used as a biomarker tool within clinical trial programs of AD for many years. Further research is currently underway with the IDEAS Study, led by the Alzheimer’s Association and the American College of Radiology (ACR). The objective of the IDEAS Study is to examine how an amyloid PET scan can help guide diagnosis and treatment of Alzheimer’s and other dementias in cases where the cause of cognitive impairment is difficult to diagnose. The results of this study could have significant impact for clinical trial applications.

Adaptive design
Developing effective treatments for NDDs whose etiology is still unclear may be a difficult task. Clinical trials for NDDs have traditionally required a large number of patients to be followed for a very long time, and the rate of success has been very low. For sponsors, adaptive designs represent a diverse approach with a common purpose of improving efficacy and clinical development, with the additional benefit of enhancing efficiency by reducing time and cost.

The FDA has provided draft guidance on adaptive design clinical trials. Adaptive design should include a prospectively-planned modification that is performed in a pre-specified manner based on interim analysis of data that is performed at pre-specified time points in a fully blinded or unblinded manner. This design approach uses accumulated data to modify some aspects of the ongoing trial, with the overall goal of preserving the validity and integrity of the trial. Adaptive design is especially useful in exploratory research and proof-of-concept studies. The most common applications of adaptive design are:

+ Sample size estimation
+ Discontinuation of dosage groups
+ Subject enrichment

Placebo exposure is a significant concern in NDD, particularly in MS, and the use of adaptive design strategies can help to reduce placebo exposure, in terms of both the number of patients and the study duration.

Subject comorbidity analyses
Comorbidity refers to the total burden of illness other than the specified disease of interest. For NDDs such as MS, physical and psychiatric comorbidities are very common. Most common comorbidities within MS are hypertension, hyperlipidemia, and chronic lung disease, while the most common psychiatric comorbidities are depression and anxiety. Many have considered these comorbidities to be associated with disease progression, lesion accrual, lower quality of life, and mortality. In addition, comorbidity in MS population affects the safety and benefit of pharmacologic therapies, including those being tested in clinical trials.

To date, clinical trials in MS have been explanatory in nature. That is, they have tested the efficacy of the intervention under ideal conditions while excluding comorbidities as an enrichment strategy. However, this strategy does not reflect the real-world population. In designing clinical trials within MS, it is necessary to consider increasing the heterogeneity of the patient population to mimic real-world populations, while still maintaining the conditions that will drive the power, sample size, and reduce...
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Site selection
NDD clinical trials can be complicated in terms of study design with the various biomarkers, adaptive design options, and comorbidities being included. With this, it is imperative to target sites that have the appropriate level of clinical and research experience within the indication of interest. Assessment of some biomarkers requires specialized equipment and staff. In addition, NDD endpoints typically require dedicated and qualified raters. It is very important to have the necessary staff on site to perform the complexities of these rigorous clinical trials and the capacity to manage the planned patient workload.

Sites should also meet requirements at the patient level. Among other things, sites need to have:

+ Access to patients
+ Skilled personnel who can discuss study details, perform informed consent, and provide patient and caregiver support
+ Flexibility to manage the required patient visits, especially in a long-duration trial where missed appointments are common
+ Experience in patient engagement, motivation, compliance, and retention

In addition, sites that have established connections with networks and advocacy groups will be better positioned for success.

Central imaging providers
Given the substantial reliance on imaging and biomarkers in NDD studies, it is imperative that sponsors and supporting contract research organizations (CROs) have established relationships and a thorough understanding of the requirements for central imaging. Niche providers within the specified biomarkers space may be assessed to support clinical trial endpoint assessment.

Comparators
In development of NDD trials, it is very important to consider design options for comparators. Specific factors to consider for inclusion of active comparators are those related to the risk of unblinding. For example, in MS, many of the treatment options have known side effects that could unblind the treatment arms. To limit the possibility of unblinding, sponsors should consider limiting or eliminating the Patient Reported Outcomes for completion. Sponsors may also consider using multiple physicians at the investigative site to assess patient adverse events and, if applicable, to examine the injection site. These physicians should be blinded from the examining physician. Obviously, this consideration increases the complexity of the study and could limit the number of sites available to participate.

Randomized, placebo-controlled studies are considered the most rigorous method of evaluating the efficacy of new treatment interventions. However, there is a growing consensus that further inclusion of placebo arms in clinical trials within RRMS is no longer ethical. It is important to interact and select countries where placebo use may be acceptable. It may be necessary to provide sound placebo justification rationale and to interact with appropriate key opinion leaders to help provide this justification. Provision of an open-label extension at the end of the placebo-controlled period could be acceptable to many agencies for placebo justification. It will also be necessary to provide appropriate educational materials to patients and caregivers to ensure they understand the benefit to risk ratio of participation in PCTs.

the “noise” that may confound the result of the clinical study. As such, sponsors should consider relaxing entry criteria to the most common comorbidities. They should also consider analyzing treatment effect, safety, and tolerability in subgroups for comorbidities.
A standardized imaging protocol may be required to ensure consistency and quality of data across the study sites, and may be required for submissions. It may be necessary for sites to qualify based upon proof of competency to adhere to the standardized imaging protocol. It will also be necessary to ensure this standardized protocol aligns with other protocol requirements and that the appropriate personnel are involved both internally and externally at the sponsor company.

In some countries, such as Germany, additional board approval may be required for studies where imaging that involves radiation is used.

**Adjudication committees**

Enrollment and endpoint adjudication committees can be used to help identify a homogeneous patient population, as defined in the protocol, to reduce variability, optimize signal detection, and decrease study risk. Since adjudication committees are blinded, they can help to assess potential safety and efficacy outcomes, as well. Sponsors should keep in mind that implementation of an adjudication committee will impact study processes, including documentation, project management, statistics, medical monitoring, and safety.

**Conclusion**

The issues and strategies discussed in this white paper can be customized for each individual sponsor, indication, and compound to result in the best possible scenario for conducting a successful study. Proactively addressing operational challenges and mitigating risk in NDD trials will bring us one step closer to one day using the word “cure” when talking about treatments for these potentially devastating conditions.
References


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