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Promoting patient and site centricity in neurodegenerative disease clinical trials

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Neurodegenerative diseases represent some of the most challenging trials, due to the unique challenges of these progressive conditions and changing needs of patients and their families. To help drug development sponsors succeed in today's clinical trial landscape, this white paper shares considerations for incorporating the patient voice into every step of drug development and contending with competition for qualified patients through patient- and site-centric practices.

Patient centricity principles

In any therapeutic area, a patient-centric approach can create greater patient engagement, recruitment, compliance and retention. Site- and patient-specific support solutions and services can also enhance recruitment diversity and retention in each trial by providing practical support to patients and their families, enabling their participation and allowing site staff to focus more on patient care and study activities. Collectively, these actions contribute to enhanced site recruitment rates while ensuring quality endpoint data.

In neurodegenerative indications, such as Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), frontotemporal lobar dementia (FTD) and Parkinson's disease (PD), there are several important, interrelated factors to examine in a study to prioritize the needs, perspectives and experiences of patients and sites throughout the clinical trial process.

1 Patient and caregiver engagement

Early engagement of patients and their caregivers can help refine the study design and endpoints, ensuring the trial is focused on both the essential safety and efficacy endpoints, as well as meaningful patient endpoints, which will help demonstrate improvement in their daily lives. Sponsors can leverage relationships with patient advocacy groups, patients and local communities to better understand their needs and expand patient outreach. These efforts of "bringing the study to the patients" (rather than bringing the patients to the study) can help increase the patient pool. Specific strategies include:

- **Study-specific patient insights:** Sponsors can gather the "voice of the patient" to better understand patients' motivations, potential barriers specific to the trial protocol, treatment preferences and needs. This critical information can also help sponsors understand the study's appeal and assess tolerance levels and support needs (including the role of the care provider). For example, input from patients and caregivers about their observed improvement with the disease can inform the design to optimize patient-reported outcomes (PROs) and improve product differentiation and development in the course of a study.

  These patient insights are "favored" by the FDA and EMA; in the United Kingdom (UK), the requirement for patient input has been formalized by the Health Research Authority into "The Participant Information Quality Standards,"[1] which have been in effect since December 2023. These standards mandate that all clinical trial submissions in the UK require evidence that those with relevant life experience have had input into the clinical trial participant information materials
- **Education:** Both the patients and their families (particularly the study partner) benefit from supportive educational materials—before patients enroll in the study—to better understand the commitment required and patient readiness for the study to improve screening efficiency
- **Ongoing engagement:** Once a patient is enrolled, it is important to keep them and their caregiver engaged in the study through two-way communication. Site staff should be available during clinic visits to focus on patient care and answer any questions. Site engagement can also be promoted through recognition of efforts and achievements, such as reaching a study milestone and sharing important study updates.

  However, with the increasing competition, complexity of trial design and site resource constraints, additional focus is needed on constructively reducing site and patient study burden to support initial and ongoing engagement. Reducing site administrative processes through integrated study systems, the option for virtual visits and specific site staff training or resource support can also help reduce the site burden in these complex trials
- **Travel considerations:** Prompt travel reimbursement and accommodations for longer visits and travel, as needed, can ease the emotional and financial burdens faced by patients and their caregivers, who may be unpaid family members. Remote/mobile visits or the use of a travel service (rather than reimbursement) can also help support the patient visit

A spotlight on patient-centric practices in frontotemporal dementia (FTD) trials

Many healthcare providers misdiagnose FTD in the earlier stages, and, as a result, many families endure a long journey to an accurate diagnosis (three to six years on average).[2] Sponsors should recognize this journey and how it impacts the patient and their family's relationship with the sites and desire for answers and solutions through a clinical trial. Some patients may have a confirmed diagnosis of FTD but still require genetic testing for the GRN mutation. Additional support and genetic counseling can help support these patients and their families.

The earlier age of onset of FTD means caregivers may be younger and may still be managing work and family commitments on top of clinic visits. Trial partner-directed materials must be carefully worded to avoid too much use of caregiver/care provider terms as most are loved ones, family and friends first. However, as FTD progresses, it becomes increasingly difficult for people to plan or organize activities so the responsibilities for complying with the visit schedule will fall more on the caregiver.

2 Study population adaptations

The patient population in neurodegenerative trials has unique needs. Depending on their condition, and the stage and severity of the disease, whether early stage, mild, moderator or advanced, a patient may have different abilities. For example, a younger patient population with mild cognitive impairment (MCI) or early Parkinson's disease (PD) may be more likely to use technology, have independence, be involved in social life and require limited caregiver/companion support. For patients with moderate to severe Alzheimer's or PD, patients may face several cognitive or mobility challenges and rely heavily on caregivers.

Sponsors can consider the use of digital endpoint collection or virtual vs. on-site visits to reduce the overall visit burden and should provide flexibility in the time of the visit to accommodate other commitments. As the patient's condition progresses, the focus may switch to the caregiver study burden, and how the condition impacts the patient's ability to comply with the study requirements. Sponsors should consider the schedule of assessments in regard to patient fatigue and cognitive ability or mobility. Modifications could include flexible visit schedules, a reduction in assessments (or carefully considering the sequencing of invasive or cognitive assessments) along with the option for a mobile health service.

It is worth noting that some patients might prefer to travel to a study site and may not be happy inviting strangers to their residences for a study visit. Here, sponsors need to be flexible in their protocol and the support solutions available, so they can be implemented as needed based on the needs and preferences of each patient.

Promoting diversity and inclusion (D&I) through patient centricity

Patient engagement efforts can also improve diversity and inclusion, which is an FDA requirement for sponsors of any Phase III or other pivotal drug study (other than bioavailability or bioequivalence studies). Our team at Fortrea recommends:

- Including key D&I questions in the site feasibility questionnaire to assess diverse patient access and experience
- Initiating diversity planning during country selection to consider the global reach of the study and recruitment of patients from different ethnicities
- Considering D&I solutions at the global level to promote inclusive research through site staff training and patient education (reflective of different health literacy levels and neurodiversity) along with culturally tailored support services to enable participation
- Utilizing real-world evidence (RWE) data with the U.S. to support site selection and ensure sites are located within areas where the targeted population resides
- Providing site training on diversity and inclusion within the SIV and investigator meeting training content. This includes educating sites on the study-level initiatives and tools available to support the recruitment of under-represented patient groups as well as best practice tips to implement

3 Study design

As mentioned earlier, early engagement with patient advocacy groups, patients and communities can help uncover research needs and inform study design. Sponsors may consider having flexibility in study eligibility when working with a narrow subpopulation. This may include allowing continued stable standard of care or medications for other comorbidities, previous treatments or even previous participation in a clinical trial.

Study design should also consider the patient visit experience. Neurodegenerative trials often have long visits with many assessments, which can be physically and mentally exhausting for patients. If possible, it can be helpful to balance the visit frequency and needs against the Clinical Outcome Assessment (COA) to understand the total number of assessments needed in one visit. Again, flexibility with remote visits, mobile health services or the use of digital eCOA/ePRO or wearables, if applicable, can ease the patient burden, resulting in greater engagement, compliance and retention outcomes.

A study's endpoints should also be suitable for the targeted population. In the early Phase I setting, sponsors should explore what is necessary versus nice to have, examine assessments that have similar utility and evaluate the timing of the various administration of assessments to align with when the patient is most likely to be relaxed and well rested.

4 Biomakers

While biomarkers can play an important role in a clinical trial and several major neurodegenerative diseases share many overlapping biomarkers,[3] sponsors must understand the patient burden of any assessment involving invasive procedures or imaging. Beyond categorizing essential versus nice-to-have biomarkers, sponsors can also consider gathering biomarker data in subsets of patients, where feasible.

The frequency of collection and measurement must not overburden the patient and caregiver, and several factors should be considered, such as radiation load, imaging agent accumulation, potential risks and discomfort to the patient when drawing cerebrospinal fluid (CSF), for example.

With the numerous biomarkers included in the studies for neurodegenerative diseases, and the high costs of some, Fortrea recommends implementing a staggered process for screening and applying prescreening processes based on the indication and available tools for remote application. For example, quick cognitive tests and blood biomarkers predictive of CSF biomarkers could be included in disease diagnostic criteria.

Sponsors could also consider the use of digital biomarkers to enhance signal detection, reduce screening failure, and avoid unnecessary burden to patients who would fail further screening, increasing the cost of study. As part of a decentralized clinical trial, the use of digital platforms and wearable devices can support these efforts by providing several services, such as symptom tracking, data collection and communication with trial staff.

5 Study treatment

Whether a neurodegenerative trial is using tablets, capsules, solutions, suspensions and/or injectables, sponsors should consider patient centricity for their chosen routes of administration. For example, for intracranial, intrathecal or IV infusions, it can be helpful to select the least traumatic catheters, needles, probes, etc., as possible. If using treatments with oral administration, the size and frequency of tablets or capsules are particularly important for patients with more severe AD or PD, as well as ensuring appropriate dose reminders and compliance aids are available. For an oral suspension, the volume of liquid to be ingested should be evaluated to determine if it is acceptable to patients along with the taste profile of the suspension.

Site-centric support

Prioritizing the needs of sites to foster engagement and collaboration helps enhance trial efficiency and reduce burden. The earlier investigators and study coordinators can be engaged, the earlier sponsors can uncover potential barriers and burdens within the protocol, enabling proactive actions to inform the study design or plans.

Sponsors can also consider using a site advisory board to inform processes and offer expert input on protocol design, patient eligibility, treatment preferences and feasibility of assessments and vendors. This can provide valuable information around their treatment preferences (and the likely patient profile for a trial) as well as the eligibility of the patient population. A site advisory board can also provide insights on the Schedule of Assessments (SOAs) and explore the potential for digital or decentralized alternatives with a study design.

The Fortrea Site Engagement and Partnership team regularly conducts site advisory boards, utilizing our site partners and key opinion leaders (KOL) relationships to curate expert groups based on topic/condition in question. This has helped shape our own internal processes and systems to better reflect site's needs and inform sponsors' trial designs.

Making an investment in patient and site centricity

Patient and site centricity in a neurodegenerative disease clinical trial represents an investment that offers returns in the form of more efficient recruitment through lower screening failure and decline rates, increased patient compliance, lower drop-out rates, and better data quality—ultimately improving chances for drug differentiation and expediting a product to market.

While patient- and site-centric practices add value to a study, these practices also need to be balanced against submission timelines and the scientific requirements and efficacy of the trial. By adopting an informed approach, sponsors can ensure their clinical trials can reduce the site and patient burden and become more relevant, inclusive and impactful for patients living with a neurodegenerative disease.

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