Worldwide Clinical Trials

The Importance of the Caregiver in Facilitating Participation in Neurodegenerative Disease Trials

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Neurodegenerative diseases are characterized by the progressive degeneration of the brain and nerves, which may affect memory, movement, or thinking. Although classified into distinct indications based on clinical phenotype, neurodegenerative diseases are a group of interlaced proteinopathies or autoimmune disorders that may share commonalities in disease course, risk factors, clinical prognosis, clinical symptoms or pathological hallmarks but ubiquitously share the same lack of cause and cure (**Table 1**). With such significant and progressive disability, patients with neurodegenerative disorders become increasingly reliant on a care partner for decision-making and activities of daily life. As a result, caregivers play a crucial role, making it essential to consider the caregiver perspective to support neurodegenerative disease trial participation. Here, we discuss some important factors and considerations in the context of running a successful neurodegenerative disease trial.

Coping with Caregiving Demands & Promoting Self-Care

A caregiver to a person living with a neurodegenerative disorder provides long-term care and support in the face of relentless progression, which may almost certainly be life-limiting or terminal in the case of some disorders. Caring for a loved one can be anoverwhelming experience, with the emotional and physical demands often leading to burnout. Taking responsibility for access to care may have a direct financial impact on caregivers and may inhibit employment opportunity or status. Countless reports indicate that providing long-term care may significantly impact quality of life (QoL) and health status, increasing the risk of depression, anxiety, and cardiovascular disease. In addition, a study has shown that poor caregiver mental health is a predictor for patient mortality in those with a neurodegenerative disease — further outlining the importance of promoting well-being in caregivers.[1]

It is important to remind caregivers about positive steps that can protect their well-being, such as a healthy diet, regular exercise, rest and breaks, good sleep habits, maintaining alternative hobbies and interests, and engaging in social circles and support networks.[2]

General Best Practices for Caregiver Support Include:

- **Resources for caregivers**, such as printed caregiver guides or informational websites, can be crucial for navigating the role of a caregiver and finding locally available support.
- **Support networks and support groups** can foster a sense of community, provide a forum for knowledge sharing, and provide a safe space for those who wish to seek comfort in the company of others.
- **Professional counseling** offers valuable coping strategies to help manage the emotional strain of caregiving.
- **Respite care** provides a much-needed break from the burden of caring for others.
- **Financial assistance programs** can help alleviate anxiety and reduce the direct financial burden of caregiving.
- **Patient advocacy groups (PAGs)** offer valuable information on healthcare policies, access to care, and provide resources designed to support caregivers.

> *Caregivers can be a close family member, such as a spouse, child, sibling, a close friend, or a professional care assistant.*

Caregivers Champion Patients' Healthcare & Trial Access

The role of the caregiver in supporting a person living with a neurodegenerative disorder to manage their healthcare is significant, especially in ensuring access investigational products through clinical trial participation. The decision to participate in a clinical trial along with the demands of the study design and operations may place an additional burden on the caregiver extending beyond their everyday responsibilities.

The diagram below indicates some elements of study conduct where the caregiver of a person with a neurodegenerative disorder has a prominent role in providing physical, emotional, and logistical assistance.

Search for Clinical Trial Availability

- Support in exploring clinical trials may motivate a patient following a life-altering diagnosis

Participation Decision & Consenting Process

- Assuring the patient and caregiver's collective ability to comply with the study requirements and commitment to long-term caregiver support
- Motivating trial participation
- Support with understanding study information and informed consent forms
- Support during study conduct
- If the study defines the caregiver's role, they may also be required to provide informed consent and attend study visits
- May be called upon to assume the role of legal representative and act on behalf of the study participant

General Communication

- Facilitate communication and understanding between patient and site especially as a patients own ability to communicate may be affected over time
- Report patient health status and level of function to site staff and clinicians outside of the clinic setting
- Be a patient advocate by asking questions and gathering information, including taking notes on behalf of the patient

Scheduling

- Support patient schedules, including the date and time of clinic visits and telemedicine appointments

Transport & Access

- Facilitate the patient's travel between home and the clinic and accompany them throughout the study visit, when transitioning between locations

Assistance with Technology

- Set up and maintain clinical trial technology such as eCOA/ePRO, wearables, and telemedicine

IP Handling & Administration

- Oversee medication management, including storage, accountability, preparation, administration, and disposal

Facilitating Patient Reported Outcomes

- Play an active role in diary completion
- Aid the patient by adding prompts to help recall COA responses, when needed
- Remind the patient to complete study tasks
- Support with QoL and functional rating

Status Updates

- Support in reporting adverse events and medical changes
- Submit a long-term follow-up, potentially reporting survival status

Caregiver Reported Outcomes

- If included, it allows for a direct role in responding to outcome measures such as burden scales

The Burden of Long-Term Care Increases Caregiver Health Concerns

Neurodegenerative disorders have some commonalities in clinical presentation, but the time course, progression pattern, and life-limiting nature are specific to the indication and may be highly heterogeneous. The chronic and progressive nature of most neurodegenerative disorders frequently affects the caregivers' own mental and physical well-being. Moreover, the increased dependency over time results in ongoing changes to the nature of demands on the caregiver, further impacting the caregiver's QoL.

When deciding to participate in clinical trials, caregivers and patients often choose to enroll at earlier stages of the disease rather than at more advanced stages. dependency on the caregiver may become more significant than was initially considered when deciding to join the trial, which could adversely impact patient retention. This further impacts the caregiver because of the emphasis on remaining in trials even if the treatment needs to be withdrawn, as this will ensure minimizing the degree of missing data. Finally, compounding the decision to enroll is a degree of altruism — the patient and caregiver are both engaged and committed to finding a cure, even when knowing the treatment may not become fully available during their disease progression.[3]

Positioning Caregivers as Research Partners with Inside Access

Acknowledging caregivers formally as integral participants in clinical studies is essential, as it ensures the integration of their needs and insights into the study design and operational strategy. While integrating patient input is already established as beneficial within clinical trial design, the significant influence of caregivers on individuals with neurodegenerative diseases necessitates a wider embrace of their experiences. Designing clinical trials should reflect the condition's specificities and consider the diverse cultural and global backgrounds of the participant population, including caregivers' unique perspectives.[4-6]

Defining a Caregiver in Protocol

The caregiver may need to be defined in the study protocol when acknowledging the reliance on the caregiver within the study design and making their participation mandatory. This may, in part, consider the caregiver's relationship to the participant, but it may also be based on the number of hours of connection within a representative period (e.g., 10 hours per week).

Health-related QoL is a significant consideration within the holistic evaluation of effectiveness. The health economics and outcome research discipline considers patient QoL evidence alongside clinical efficacy and healthcare utilization. Adopting caregiver measures into clinical trial protocols adds perspective on the impact of treatment. It also serves to formally enroll the caregiver into the study as a participant whose opinions are collected and reported as part of the clinical trial. Caregiver burden scales assess the impact on the caregiver's life's physical, emotional, social, and financial aspects. Some examples include:

- The Revised Scale for Caregiving Self-Efficacy evaluates confidence in coping with caregiving challenges.[7]
- The Zarit Burden Interview measures the caregiver's perception of the caregiver's role, health and well-being, and the patient's dependency on the caregiver.[8]

Caregiver Engagement the Worldwide Way

Given the caregiver's critical role in study enrollment, retention, and data collection, it is important to recognize the significant value of the caregiver's contributions within the study.

We work to create a study ecosystem that engages the community to support the caregiver role. This typically includes the investigators and PAGs, who consider the holistic support offering, emphasizing general support and emotional, operational, and financial aspects.

General Support

Worldwide is dedicated to improving caregiver's well-being, which in turn strengthens their ability to provide crucial support. We achieve this by leveraging existing resources designed for caregivers offered by clinical sites and community groups resources provided for study participation. We additionally offer education and training programs to equip caregivers with the necessary knowledge and skills and provide resources containing:

- Trial requirements: include a caregiver-directed study brochure and a caregiver section on the study website
- PAG support: we provide a list of relevant organizations, their patient resources, contact details, and upcoming events. We suggest contacting PAG in advance to ensure they are aware of the study and the caregiver and patient needs
- Supplemental information about the indication
- Health and guidance for caregiver well-being
- Visit reminders and study applications that trials can share with caregivers to support their role in caring for the patient

Beyond general well-being, we also understand how important it is to recognize the caregiver's efforts as they experience daily challenges beyond those associated with trial participation. Empathy and recognition can help improve caregiver wellness and resilience, fostering a better overall experience. This includes recognizing the caregiver by considering additional emotional factors.

Emotional Support

A key to participation is building trust and confidence in the selected study. We achieve this by ensuring that our studies are discoverable through the leading indication-specific navigation tools, that they are conducted by leading research sites and are familiar to local community leaders. We review and partner with PAGs to identify the availability of local community resources, including counseling and support networks specific to caregiver needs for the respective condition. Beyond resources, we prioritize how we engage caregivers through the tone of study communications. Design, please put this sentence after the first sentence of this section.

Operational Factors

We select sites based on experience, capabilities, and geography to ensure professional and compliant study conduct and access to the trial. In addition, we recommend offering full-service concierge travel to the patient and caregiver that accommodates the patient's mobility constraints, reducing any potential transportation-related stress and complications.

Following the onset of the COVID-19 pandemic, clinical research has made strides and learned many lessons about increasing the role of hybrid decentralized trials (DCT).[9] We support increased hybrid DCT, but a key consideration for any trial is if the available technology provides data equal to or surpasses that collected from a site visit. Finally, supporting caregivers in embracing technology and ensuring adequate training is critical for participant retention and optimal data collection.

Financial Support

From a financial perspective, providing caregiver stipends as part of the study budget, including reimbursement for vacation days taken to attend on-site clinic visits, will likely increase participation and retention and reduce caregiver stress. In addition, timely reimbursement for any costs incurred due to participation, including meals, childcare, tolls, and parking, is important to ensure no financial burden for patients or caregivers.

Caregivers are the Cornerstone

In neurodegenerative disease trials, we cannot overstate the role of the caregiver. Caregivers are pivotal in facilitating trial participation, ensuring protocol adherence, and supporting patients' well-being. The emotional, physical, and financial burdens caregivers bear demand recognition and support. By formally acknowledging and integrating the caregiver's role into clinical trial design, we can enhance patient and caregiver experiences, improving compliance and more robust data collection. The success of clinical trials in neurodegenerative disorders hinges on this holistic approach, which values the contributions and perspectives of caregivers.

Prioritizing caregivers in neurodegenerative diseases involves acknowledging their indispensable role and providing comprehensive support systems to mitigate the burdens they face. Researchers, clinicians, and policymakers must collaborate to ensure the integration of caregiver perspectives into study protocols and the allocation of appropriate resources for their support. Moreover, study sponsors should make provision to ensure that trial data, no matter the outcome are reported and shared with the patient and caregiver out of respect for their motivations and efforts in participating in neurodegenerative research.

Table 1: Fact Box on Neurodegenerative Disorders

Indication/Clinical Diagnosis	Anatomical Involvement	Pathological Hallmark	Clinical Presentation
Alzheimer's Disease (AD)	Initially affects the entorhinal cortex and hippocampus impacting memory. Other regions become involved as the disease progresses such as the cerebral cortex, the frontal lobe, the temporal lobe, and the parietal lobe.	Accumulation of the protein beta-amyloid outside neurons and twisted strands of the protein tau inside neurons is accompanied by inflammation and atrophy of neurons and brain tissue.	Usually starts slowly with most common early symptom being recent memory loss. Progressively worsens with symptoms including cognitive decline, agitation, disorientation, mood swings, loss of motivation/self-neglect, behavioral issues, and deficits in language skills. Gradually, bodily functions are lost, the speed of progression is variable but ultimately fatal within 3-12 years after onset of symptoms.
Lewy Body Dementia (LBD)	Affects neurons in both the central nervous system and the autonomic nervous system. Dementia can be a result of involvement of the cortex.	Lewy bodies are abnormal aggregations of the protein alpha-synuclein.	Umbrella term for two similar and common subtypes of dementia: Dementia with Lewy bodies and Parkinson's disease dementia. Symptoms may include memory impairment, confusion, hallucinations, delusions, or reduction in attention/alertness. Additionally, Parkinson's disease-like symptoms (rigid muscles, slow movement, tremors, erratic movement) are experienced along with dizziness, falls and sleep disorders such as REM sleep behavior disorder. Typically associated with a shorter lifespan.
Corticobasal Degeneration (CBD)	Degeneration of the corticobasal region which is responsible for movement movement control and information processing.	Cell loss thought to be due to toxic accumulation of tau.	Symptoms may include poor coordination, loss of movement, rigidity, poor balance, unnatural posturing of the muscles, muscle jerks, difficulty swallowing, intellectual (cognitive) impairment, and speech impairment. May develop serious secondary complications such as clotting or sepsis which may often lead to death.
Frontotemporal Dementia (FTLD)	Progressive degeneration of the brain's frontal and temporal lobes.	Histological subtypes defined by protein aggregates of either tau, TDP43 or FUS.	Symptoms may include changes in social and personal behavior, disinhibition, apathy, blunting and dysregulation of emotions, along with deficits in both expressive and receptive language. Fatal within 2-10 years after osymptom onset.
Amyotrophic Lateral Sclerosis (ALS)	A progressive disorder which affects the upper motor neurons and lower motor neurons.	May be sporadic or familial. A pathogenic mutation associated with ALS is identified in 10% of cases. Various hypothesized pathologies including glutamate excitotoxicity, mitochondrial dysfunction and oxidative stress, inflammation, lysosomal-endolysosomal, proteostasis failure, vesicle transport defects, cytoskeletal disturbance and axonal transport defects, microglia dysfunction, DNA repair, RNA processing and nucleocytoplasmic transport defects. Cytoplasmic protein aggregates include TDP43 (97% of cases), SOD1 or FUS.	The loss of motor neurons causes the muscles under their control to weaken and waste away, leading to paralysis and death, usually due to respiratory failure. Symptoms may include loss of motor control in hands, arms and legs, tripping and falling, bulbar symptoms with difficulty speaking, swallowing and/or breathing, persistent fatigue, twitching and cramping of the muscles as well as cognitive and behavioral changes. Fatal within 3-5 years after onset of symptoms.
Parkinson's Disease (PD)	Affects a deep brain region called the substantia nigra. Later stage involvement of the cortex.	Aggregates of the protein alpha-synuclein which are thought to cause degeneration of dopamine producing nerve cells.	Affects both the motor system and non-motor systems. Common symptoms include tremor, slowness of movement, rigidity, and difficulty with balance. In advanced stages, additional features may develop including falls, dementia and neuropsychiatric problems such as sleep abnormalities, psychosis, mood swings, and behavioral changes. Near-normal life expectancy.

Multiple Sclerosis (MS)	Damage to the insulating covers of nerve cells in the brain and spinal cord. This damage disrupts the ability of parts of the nervous system to transmit signals, resulting in a range of signs and symptoms.	Three main characteristics of MS which interact and result in neurodegeneration include the formation of lesions in the central nervous system (also called plaques), inflammation, and the destruction of myelin sheaths of neurons. Damage is believed to be caused, at least in part, by an autoimmune response primarily mediated by T-cells.	New symptoms may either occur in isolated attacks (relapsing forms) or build up over time (progressive forms.) In relapsing forms, symptoms may disappear completely between attacks (with some permanent neurological signs more likely to remain in advanced disease). In progressive forms, there is a continual functional decline over time. Prominent symptoms include double vision, vision loss, eye pain, muscle weakness and loss of sensation or coordination. Reduced life expectancy by approximately. 7-14 years, but a full and active live can be fulfilled with proper management.
Neuromyelitis Optica Spectrum Disorder (NMOSD)	Affects the optic nerve (optic neuritis) and the spinal cord (myelitis).	An autoimmune disorder in which acute inflammation results in neurodegeneration.	Inflammation of the optic nerve and/or optic chiasm may lead to varying degrees of visual impairment with decreased visual acuity, visual field defects, or loss of color vision (typically occur prior to formal loss and may be in isolation). Myelitis causes spinal cord dysfunction, which can result in muscle weakness, paralysis in the limbs, lost or reduced sensation, spasms, loss of bladder and bowel control, and erectile dysfunction.
Progressive Supranuclear Palsy (PSP)	Affects both neurons and glial cells.	The neurons display neurofibrillary tangles, which are clumps of tau protein, a normal part of a brain cell's internal structural skeleton. These tangles are often different from those seen in Alzheimer's disease	Common early symptoms are changes in personality and behavioral symptoms including apathy, a lack of inhibition, anxiety, and a profound state of unease or dissatisfaction. The condition leads to later symptoms including loss of balance (lunging forwards when moving, fast walking, falls and bumping into objects/ people), slowing of movement, difficulty moving the eyes (vertical), cognitive impairment, slurring of speech and difficulty swallowing. Fatal, within 7-10 years after onset of symptoms.
Multisystem Atrophy (MSA)	Affects the basal ganglia and inferior olivary nucleus	Characterized by a prion of the alpha-synuclein protein.	Symptoms may include tremors, slow movement, muscle rigidity, postural instability, ataxia, and palsy of the vocal cords. Many people affected by MSA experience dysfunction of the autonomic nervous system, which commonly manifests as orthostatic hypotension, impotence, loss of sweating, dry mouth, urinary retention, and incontinence. Fatal within 6–12 years after symptom onset.
Huntington's Disease (HD)	Predominantly affects the basal ganglia	Huntington's disease is caused by a mutation in the HTT gene, following an autosomal dominant inheritance pattern. Specifically, expansion of trinucleotide CAG repeats of cytosine-adenine-guanine in the gene coding for the huntingtin protein results in abnormal mutant protein (mHtt), which causes progressive degeneration of nerve cells in the brain through various possible mechanisms.	Huntington's disease causes movement, cognitive, and psychiatric disorders. Clinical features and progression rates are heterogeneous. Movement disorders include chorea tremors, rigidity, slow or abnormal eye movements, impaired gait, posture, and balance, and difficulty with speech and swallowing. Cognitive disorders include inability to process thoughts, problems with organizing, prioritizing, or retaining focus on tasks, difficulty in learning new information and finding words to speak, getting stuck on thoughts, behavior, or action, lack of control over impulses, being unaware of one's own behaviors, and dysgraphia. Psychiatric disorders may include depression and/or mania, irritability, social withdrawal, insomnia, fatigue, suicidal thoughts or tendencies, and apathy. Reduced life expectancy, fatality within 10-30 years after onset of symptoms usually due to infection or injury from fall.

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