WHITE PAPER

SHIFTING TIDES IN DEMENTIA RESEARCH

Strategic considerations for regulatory, operational, and commercial success

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According to the World Health Organization (WHO), more than 50 million people around the world currently live with dementia, and that number is growing at a rate of 10 million per year. By 2030, the WHO projects that the worldwide population of individuals with dementia will reach 82 million – and will climb above 150 million by 2050.¹ Of the population suffering with dementia today, the WHO estimates that 60-70% suffer from Alzheimer’s disease (AD). The remaining 30-40% – representing between 15 and 20 million people – suffer from one or more of the neurodegenerative conditions illustrated in Figure 1, including frontotemporal dementia (FTD), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), dementia with Lewy bodies (DLB), Parkinson’s disease (PD), multiple system atrophy (MSA), or one of the many subtypes of each of these conditions.

A FOUNDATION UPON WHICH TO BUILD

Consider the challenges associated with studies focusing on the behavioral variant of frontotemporal dementia (bvFTD). It is the most common of the five subgroups of FTD, but individuals with bvFTD are frequently misdiagnosed as having AD. Both conditions are progressive and involve complex genetics. Both present phenotypical variability and involve a heavy caregiver burden. Protein aggregations within the CNS associated with progressive atrophy of frontal and anterior temporal regions of the brain are present in each, and both are outwardly characterized by alterations in behavior, language, cognition, and physical abilities.

Yet, there are subtle but important differences between bvFTD and Alzheimer’s disease. In bvFTD, the behavioral alterations are more pronounced than the language alterations, which are more pronounced than the cognitive alterations or the physical signs. Conversely, in AD, the cognitive alterations typically present first and assume primacy in clinical trial design and study implementation. Therapeutic agents correspondingly have different molecular targets, and all aspects of a clinical trial – from site selection to study design, staffing, assessments, and data collection – must be shaped toward this unique phenomenology.

Begin with a site focus

When supporting studies exploring new areas of dementia research, such as those associated with interventions for bvFTD, it is critical to engage sites and professionals already associated with the established research community in preference to community care centers, even if the site’s experience lies in areas other than the target condition. The site’s experience in diagnostics and assessments for a related condition, such as AD, provides a springboard into the critical conversations about novel assessments and interventions for other conditions.²

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Given the burden that caring for individuals with dementia places on both the health care system and caregivers, research and development efforts now extend beyond AD to explore a mosaic of syndromes, each of which presents unique and significant challenges, in part because so much remains unknown about the pathophysiology, clinical presentation, and course of these conditions. Understanding each of these domains is crucial to the development of effective pharmacotherapy at a foundational level. This publication stands in service to that initiative, reflecting three decades of applied clinical research in which innovative pharmacotherapy has been evaluated in increasingly refined patient phenotypes.
For example, trialists involved in relatively less common presentation of neurodegenerative disorders are often academics providing services in a tertiary care setting. These investigators are familiar with constructs underlying disease pathophysiology and are uniquely suited to contribute to trial-mandated procedures for assessments and patient management for those conditions that do not enjoy a rich pedigree of clinical research. Early interactions with experts of this caliber help to identify best practices that can be incorporated into protocol design and operations. Correspondingly, individuals representing the CRO and the sponsor need to be experts in their own right – well-credentialed academically, deeply steeped in the science, and familiar with the latest body of evidence regarding biomarkers and the neuroimaging modalities that might be useful.

It is worth noting that certain operational dynamics in trial conduct for a novel neurodegenerative therapy closely resemble those found in other areas of research, such as cardiovascular outcome trials (CVOTs). For this reason, trial designers and operational experts in neurology have found it useful to consult with personnel who specialize in other fields that, at first blush, appear to be unrelated. Trial designers, for example, have drawn useful insights for bvFTD trials from CVOT trials in areas such as vendor coordination in a multicenter, multinational environment and the creation of common touchpoints for different study-related committees (including imaging, biomarkers, data management, biostatistics, IP management, the scientific advisory board, and a publication committee). Design and operational staff who specialize in orphan disease research provide fungible insight regarding patient identification and accrual.

Finally, it is critical that personnel on the CRO side of a

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**WORLDWIDE CLINICAL TRIALS: A HISTORY OF SUPPORTING DEMENTIA RESEARCH**

From its inception, Worldwide Clinical Trials has been on the forefront in support of clinical research in neurodegeneration, most prominently AD and related disorders. Team members have been involved in the development of clinical assessment methodology, including the first commercial computerized neuropsychological (NP) test; the first commercial use of cerebrospinal fluid/plasma pharmacokinetic/pharmacodynamic (CSF/Plasma PK/PD) modeling, the first industry-sponsored multinational studies for cholinesterase inhibitors; and the first industry-sponsored studies in prodromal Alzheimer’s disease. Team members have also contributed to the evaluation of a large number of compounds in approximately 15 different classes reflecting increasingly sophisticated pharmacological concepts (Figure 2). From these engagements, a rich library of more than 500 publications focusing on innovative clinical research methodologies has emerged applicable to an international environment. The experiences and the insights presented in these publications inform the organization’s day-to-day activities and help support both academia and industry to become increasingly effective in developing solutions for neurodegenerative diseases.

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**Figure 2: Worldwide has been involved in studies associated with numerous AD-related technologies.**

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study possess a thorough operational appreciation of the challenges associated with study operations in a complex study environment. Real-world studies never take place in a vacuum. They take place in sites where many other activities – many with competing priorities regarding clinical care – take place simultaneously. It is incumbent upon the trialists and operational subject matter experts to ensure that the site’s other areas of service delivery are not impeded by study activities (or vice versa) and that protocol-mandated procedures are complementary to clinical care.³

**Considerations for Patient Eligibility and Retention**

Experience with studies evaluating phenotypes of AD and bvFTD have produced insights that can be useful in the determination of patient eligibility and in planning for patient retention in any dementia study. A wide range of screening and assessment protocols exist, including clinician- and patient-based rating scales to biomarker signatures and neuroimaging technologies, but this plethora of options can both simplify and complicate screening. Positioning protocols appropriately within a screening algorithm requires both a thorough understanding of the tools and what insights they can deliver.

Potentially substantive pharmacokinetic or pharmacodynamic interactions between a test agent and another medication also may play an important role in patient eligibility. Many potential participants in a dementia trial are elderly and have comorbidities and concomitant medications that cannot be restricted within protocol. Interactions between the test agent and another medication may introduce considerable complexity into study design and trial operations, which may either jeopardize accrual or significantly impact the generalizability of the emerging results. While it remains the responsibility of the sponsor to develop the preclinical tests to determine possible drug/drug interactions (particularly when the IP involves a small molecule), it remains the CRO’s responsibility to determine what impact a potential interaction would have on study feasibility, particularly in a multinational setting where diverse standards of care may exist.

It is also important to consider the matter of managing the neurobehavioral disturbances that can occur in a longer-term clinical trial. This is of critical importance for studies involving a rapidly evolving disease like bvFTD. A patient’s behavior and compliance will likely decline during the course of the study, and this may lead to concerns that patient and caregiver may be unable to complete the trial in a manner fully compliant with the study’s original mandates (e.g., procedures or the introduction of psychotropic medications that are required for patient management).

Some of these same issues reassert themselves when it comes to patient retention. New technologies can both complicate and facilitate ongoing assessment and measurement. Depending on the design of a study and the plans for patient monitoring, there may be questions about where assessments will be conducted (e.g., within clinic or at home). Those that are highly operator-dependent will most likely be conducted in a clinical care setting, but others may be amenable to being conducted in-home, via telehealth, or via some other engagement modality. If assessments may be conducted in-home, this raises other demands regarding training and credentialing for staff.

Ultimately, design is linked to operations, and considerations about patient eligibility and retention must be factored into study design and operational planning from the earliest days. All these considerations can add complexity in a study, even one taking place in a relatively small number of sites in a single country. In a large interventional study involving multiple geographies, languages, cultures, and local standards of care, the challenges can grow exponentially.

**Novel assessments, uncertain clinical interpretation**

Because of the variations in patient presentation existing across memory, language, and other cognitive behaviors - in areas ranging from executive function and memory
to disease severity, self-care, and motor impairment – the standardization of clinical trial assessments in a dementia trial has been a recurrent theme. Particularly in a multinational, multicenter study, assessments can be heavily influenced by operator characteristics, so standardized approaches are implemented to enhance signal detection. This is particularly important where clinical measures are increasingly prolific and where newer assessments, including assessments focusing on social cognition and personality changes or emerging assessments intended to monitor a patient’s sensitivity to pleasant and unpleasant scents, heat, cold, and pain, have gained increasing currency.

If an assessment is novel, the clinical implications of captured data may be unfamiliar to clinicians who are not yet accustomed to working with the assessment. For this reason, ensuring the integrity of captured data – from the point of its acquisition to its eventual analysis – has become an overarching remit in large-scale international multicenter trials. Protocols must be in place to analyze captured data in real time and flag any results that appear out of bounds. Individuals with expertise in data management and clinical assessment must review the flagged data and compare the recorded results to source documents to ensure that the results were recorded accurately. If discrepancies in the methods of data acquisition are determined, preemptive site training must occur in advance of any future assessments scheduled to take place onsite.

On this latter point, it is worth noting that some of these newer technologies produce a montage of measures, each of which attempts to satisfy the data requirements of different stakeholders. The primacy of one assessment over another, and the sequence of their acquisition are critical points to consider, particularly when dealing with patients with cognitive impairments. When incorporating unique neuropsychological assessments, for example, a dedicated team must be embedded within the clinical operations group that can focus on rater credentialing, training, and surveillance mechanisms.

Finally, it is critical that any assessments that a clinician intends to share with a patient be prepared in a way that is easy for patients (and/or their caregivers) to understand. This can be a challenge, given differences in language and culture that might affect interpretability. In a multinational study, this may warrant a separate work stream, addressing translation, validation, and the propriety of the assessments for a given culture.

**AT THE FRONTIER OF DEMENTIA RESEARCH**

In neurodegenerative disorders, past is indeed prelude, and experience supporting AD, vascular dementia, and bvFTD studies provides a solid foundation upon which to build support for a wide range of emerging dementia research areas. AD and FTD (all types) are tauopathies, neurodegenerative disorders characterized by abnormal deposits of tau protein as neurofibrillary tangles (NFTs) in the cortical areas of the brain. But AD and FTD are not the only tauopathies. Others include corticobasal degeneration (CBD) as well as progressive supranuclear palsy (PSP) and its three subtypes – PSP with corticobasal syndrome (PSP-CBD), PSP with parkinsonism (PSP-P), and PSP with progressive non-fluent aphasia (PSP-PNFA). To differing extents, all these tauopathies lead to executive dysfunction, progressive aphasia, disinhibition, compulsive disorders, eating disorders, and changes in artistic productivity.

**A complex molecular framework**

Separate from these tauopathies, though, are neurodegenerative disorders falling under the heading of synucleinopathies. These conditions are characterized by fibrillary aggregates of a-synuclein protein in the cytoplasm of selective populations of neurons and glia in the subcortical areas of the brain. Synucleinopathies present as fluctuations in motor and cognitive symptoms (including hallucinations, illusions, and delusions), eating disorders, REM-related sleep disorders, and autonomic system failures. Parkinson’s disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA) are all examples of synucleinopathies.
Because of the nature of the known pathophysiologies within these phenotypes, there are overlaps as well as distinctions. Some have greater degrees of Parkinsonian motor disorders (bradykinesia, rigidity, and tremors); others have greater degrees of cognitive impairment. Although the outward presentation of many of these disorders may be similar, an important factor that distinguishes the tauopathies and synucleinopathies is that patients afflicted by a tauopathy are very rarely found to present an excess of α-synuclein; similarly, patients afflicted by a synucleinopathy rarely present any indication of excess tau.

The proper evaluation of novel therapeutic agents, which increasingly are based upon targets rather than phenotypically based drug discovery algorithms, therefore, require an appreciation of potential distinctions extending from the molecular target through various clinical phenotypes.

Contingent upon the source, 60-70% of all dementia diagnoses involve AD. DLB may account for 20-30% of dementia diagnoses. But, as suggested in Figure 4, there is a significant degree of overlap where these diagnoses occur.

In the portion of the diagram where NFTs, α- and β-senile plaques, and Lewy bodies intersect, one may find neurodegenerative conditions that seem as though they could involve tauopathies and synucleinopathies, and this is where real-world experience and knowledge of the key disease characteristics becomes important. Specifically, there are no clinical guidelines for making a diagnosis of DLB, nor are there biomarkers that can distinguish DLB from AD or Parkinson’s disease dementia (PDD). A patient who presents the cognitive and behavioral deficits associated with AD but who also has Lewy bodies is more likely to have DLB or PDD.

In the absence of a specific biomarker signature providing a precise diagnosis, clinical acumen becomes the primary method of distinguishing the conditions. To determine whether the patient is more likely to have DLB or PDD, it is important to understand the progression of the disease in that individual. If dementia appeared before the characteristic features of parkinsonism, then the patient is more likely to be afflicted with DLB. If the parkinsonism appeared before the dementia, the patient is more likely to be suffering from PDD. As has previously been stated, emerging clinical targets broadly defined under “neurodegeneration” accentuate the value of involving investigators who have had relationships with study participants that precede the here and now of a clinical trial.

Limited prior clinical art

While the progression of DLB and PDD differ, the conditions evolve into same phenotype over time, which is important because it suggests that any new drug development targeting DLB or PDD might include patients with either condition over the duration of the program. However, this has not been the case over the past 20 years. Between 2000 and 2020, 73 interventional studies have targeted DLB, but only 31 also identified PDD as a target. Only 65 interventional studies expressly focused on PDD during the same period, and only 28 of those also indicated DLB as a target.

DPB and PDD are the most common neurodegenerative
disorders after AD. Yet, between 2000 and 2020, when fewer than 60 interventional studies targeted both DLB and PDD, more than 2,000 interventional studies targeted AD. Four drugs are currently used to treat DLB and PDD – rivastigmine, donepezil, galantamine, and memantine, but of those four, only rivastigmine is FDA approved for treatment of PDD. Donepezil has been approved for the treatment of DLB in Japan and the Philippines, but it only used off-label in the U.S. and E.U. Galantamine and memantine, too, are used off-label for treatment of DLB and PDD. It is worth noting that none of these drugs were expressly developed to treat DLB. They were found to be useful in AD and Parkinson’s disease scenarios and their off-label use has been extended to DLB.

On the importance of diagnostic acumen

Insofar as those suffering from DLB and PDD form such a significant segment of the millions of people suffering from dementia, comparatively few trials focusing on DLB and PDD are underway. Yet, as noted earlier, there have been historical difficulties in diagnosing DLB. The clinical presentation of DLB can include six different syndromes, including autonomic, sleep, behavioral, and movement disorders, cognitive impairment, and fluctuation of attention that can manifest as delirium. The severity of the symptoms associated with each of these syndromes can lead to a misdiagnosis. Excessive daytime sleepiness, restless leg syndrome at night, or a REM sleep behavior disorder might lead a clinician to diagnose only a sleep disorder; a pronounced gait impairment, parkinsonism, or a history of falls might lead to a diagnosis of a movement disorder. Particularly if any of the sleep disorders are overshadowed by the movement disorders, a clinician not trained to look for a constellation of syndromes occurring together may diagnose DLB. This is where a tool such as the Lewy Body Composite Risk Assessment can be extremely useful within a clinical trial setting. It is an inexpensive assessment that can help clinicians diagnose DLB more effectively. In a clinical trial setting, the Lewy Body Composite Risk Assessment can help trialists reduce screen failure rates before consent – and without requiring more aggressive or expensive screening techniques such as imaging.

It should be noted that conducting a Lewy Body Composite Risk Assessment is best done in-person and best done in the presence of someone acting in a caregiver capacity who can provide answers when the individual being assessed cannot (or cannot reliably) do so.

That being said, how effectively a tool like this can be used in a telehealth or telephone-based interaction – such as those increasingly taking place during the COVID-19 pandemic – remains another of the many unanswered questions that hover in the realm of dementia and neurodegenerative research.

In the case of DLB, dementia is the central feature; it must be present for any diagnosis of DLB. In addition, there are core features and indicative biomarkers, as well as supportive clinical features and supportive

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**Figure 6: Diagnostic Criteria for Dementia with Lewy Body, based on McKeith et al., 2017**

<table>
<thead>
<tr>
<th>Essential</th>
<th>Core Features</th>
<th>Indicative biomarkers</th>
<th>Supportive Clinical Features</th>
<th>Supportive biomarkers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dementia</td>
<td>- Fluctuating cognition with pronounced variations in attentions and alertness - Recurrent well-formed visual hallucinations - REM sleep behavioral disorder (RBD) - Spontaneous parkinsonism</td>
<td>- Low dopamine transporter uptake in basal ganglia (SPECT or PET) - Low uptake in 123I-MIBG at myocardial scintigraphy</td>
<td>- Neurotic sensitivity - Automatic dysfunctions, falls - Other hallucinations, delusions - Depression, anxiety, apathy - Hypersomnia, hypnagogia</td>
<td>- Low PET/SPECT perfusion - Posterior slow wave ECG</td>
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Probable DLB

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biomarkers that, in various combinations, can help drive a determination about whether DLB is actually the proper diagnosis. For example, DLB is the probable diagnosis if dementia is accompanied by two of the findings in the core features field in Figure 6. Similarly, the presence of dementia, one core feature, and one indicative biomarker can also lead to a “probable DLB” diagnosis. However, if the assessment finds dementia and a core feature without also finding an indicative biomarker, then the “probable DLB” diagnosis becomes merely a “possible DLB” diagnosis. Similarly, if there is dementia and one item from the indicative biomarkers column – but nothing from the core features column – then a DLB diagnosis is “possible” but not “probable.” The above diagnostic discussion illustrates the primacy that is placed upon investigators who are skilled diagnosticians in therapeutic areas that thus far have provided little routine guidance for patient indemnification and accrual.

On the role of “biomarker signatures”

Emerging diagnostic methodologies using biomarkers have begun to show promise. While direct biomarker evidence for DLB remains unavailable, several biomarkers appear to provide indirect evidence: these include the use of myocardial scintigraphy and a 123I-MIBG tracer to measure the early heart/mediastinum (H/M) ratio; SPECT or PET imaging to detect reduced DAT uptake; and polysomnographic confirmation of REM sleep without atonia. But, these are expensive tools for early assessment and may be better used after the Lewy Body Composite Risk Assessment has been conducted and after the diagnostic assessment criteria have been used to determine the likelihood of a DLB diagnosis.

A focus on safety, not just efficacy

Ultimately, all these elements highlight the challenges facing any research reaching beyond the more well-trodden paths associated with AD and its immediately relevant phenotypes. A wide range of neurodegenerative disorders exist, yet they present in overlapping ways that can confound researchers. Subtle distinctions are increasingly important when the target is a discrete molecular entity.

Tools exist that can help screeners make a more well-founded diagnosis of a condition such as DLB, but such a diagnosis requires substantial clinical knowledge as well as adequate time to gather a full history. Work related to the identification of biomarkers is encouraging but inconclusive. Increasingly sophisticated technologies are helping deliver equally nuanced insights into disease presentation, but how and when to use these technologies and how to interpret the results they present are questions that remain to be answered.

These challenges are critical not only because they make it more difficult for researchers to study the effects of medications on individuals afflicted with a specific condition but also because improper identification of individuals with distinct conditions can lead to serious problems. Particularly in a condition such as DLB, for example, one must keep the interrelationship of the presenting syndromes in mind. One drug may have a positive effect on cognition but may leave the door open to an increase in frequency or severity of hallucinations.

As an operating rule of thumb, if the alleviation of one syndrome associated with DLB is the primary objective of a study, all other syndromes must be monitored simultaneously for safety before the efficacy of the intervention is determined.

That need can complicate the design of a study and the nature of patient monitoring and follow-up, but it cannot be ignored.
SUMMARY

Because of phenotypic variation, there can be significant overlap between different patient subtypes under the broad umbrella of neurodegeneration. Therefore, the clinical evaluation of a novel biological entity, chemical entity, or advanced therapy medicinal product will need to be optimized based upon eligibility criteria within the protocol, which largely remain incompletely defined for many of the disease subtypes. These criteria must be mapped against the clinical care of patients, accompanied by exceptional diligence regarding diagnostic acumen, the application of unique assessments, and the convergence of agreement that must occur in multicenter clinical trials.

At the emerging frontier of research in neurodegeneration, study conduct can be optimized by creating a matrix organization in which subject matter experts from different research, technical, and operational domains are included within efficient project teams. Study conduct can also be enhanced by drawing on operational models in other therapeutic areas, such as cardiovascular outcome studies, orphan disease development, and other areas of comparable complexity, which likewise require the coordination of multiple contributing stakeholders with different areas of subject matter expertise. Critical experiences within those areas are fungible across the evolving landscape of dementia research and should not be discounted.

With each incremental advance in understanding about the pathophysiology of different neurodegenerative diseases, new questions arise and new avenues of exploration appear. Those organizations long dedicated to advancing methods in medicine and a strategic approach to engagement – at every level – are well-poised to help advance the frontiers of dementia research.
REFERENCES


