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OVERCOMING COMPLEXITIES IN ALZHEIMER'S AND NEURODEGENERATIVE CLINICAL TRIALS

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Clinical development faces significant challenges, particularly in neuroscience, with notably high attrition rates and one of the lowest success rates across therapeutic areas.[1] The complexity in regulatory expectations, study design, participant selection, therapeutic platform, mechanism of action, route of administration and outcome assessment are preeminent drivers of these figures.

In the realm of neurodegeneration, including well-known diseases like Alzheimer's (AD), Parkinson's (PD), motor neuron disease (MND) and less-talked-about indications such as Huntington's (HD), atypical parkinsonisms, frontotemporal dementia (FTD), prion diseases, among many others, there are few approved and effective therapeutic interventions.

With approximately 56.9 million people worldwide living with AD and other dementias—projected to rise to 78 million by 2030 according to the WHO—along with 273 thousand living with MND and 11.8 million with PD, the need for effective treatments is critical.[2]

Given the limited approved and effective medications, the epidemiology and natural history of these conditions, and the profound impact on patients, families and society, there is a large unmet need for new treatment options. This article will explore the challenges of AD and neurodegenerative clinical trials, highlight recent successes in the field, and discuss strategies for achieving success in these trials.

KEY CONSIDERATIONS IN ALZHEIMER'S AND NEURODEGENERATIVE CLINICAL DEVELOPMENT

Understanding the complexities of AD and neurodegenerative research is essential for the successful execution of trials.

One main challenge is knowing the physiopathology of these diseases and the causative agents. While clear for some diseases, for many neurodegenerative indications it is still in debate what are causative agents, downstream events, and epiphenomenon. A clear relationship between the potential target, the disease physiopathology, the mechanism of action and exposure are critical to the success of a program; data informing these aspects can be used from discovery and preclinical development to predict the likelihood of success in clinical development.

Another challenge is case selection: ensuring the selected participants have the appropriate pathology (target) that the investigational product (IP) aims to modify. Clinical diagnostic criteria have been traditionally used with this aim, but these are known to have significant false positive rates in several indications, such as AD and PD, which can dilute the treatment effects of potentially effective interventions.[3,4] The scientific field and regulators are moving towards using objective correlates of pathologic abnormalities, including biofluid (e.g., blood alpha-synuclein in PD)[5], imaging (e.g., caudate volume in HD)[6] and electrophysiological (e.g. electromyography in MND)[7] biomarkers for selection, enrichment and stratification. An added benefit is that these tools not only help with obtaining a study population with increased likelihood of presenting the target of interest, but also ensure a more homogeneous study population optimising statistical power of small early development studies.

A third and somewhat related challenge is the sometimes-limited accumulated understanding of the sequence of pathophysiologic processes and its correlation with the disease phenotypic manifestations, and its critical relevance to select the optimal time to pursue treatment. Unlike oncology, where current standard of care often initiates as early as an abnormal macrobiologic process is identified, in neurodegeneration we often expect investigational treatments to modify the disease course many years, sometimes decades, after the initiation of the pathophysiologic processes. Unfortunately, the rarity of some indications, the subtlety of their biologic manifestations, our inability to detect early changes and to track them down, and ethical and logistic reasons have precluded attempts of earlier intervention.

Finally, is the ability to detect and measure treatment effects accurately with its nuances in early and late development. While proof of target engagement frequently relies on biomarker change, essential-to-marketing clinical efficacy is expected to be shown through how the participants feel, function, or survive, and in every time less exceptional cases, by biomarker correlates of clinical efficacy (i.e., surrogate outcomes). Despite the importance of outcome assessment tools in clinical development, these are frequently sub invested aspects of study methodology, leading to inefficient go/no-go decisions and potential regulatory/payer/prescriber uncertainty.

RECENT SUCCESSES IN NEURODEGENERATIVE CLINICAL DEVELOPMENT

Despite the challenges, there have been recent advancements in the field offering new hope.

A notable success story is the one of spinal muscular atrophy (SMA), a largely paediatric and genetic form MND. In a decade, SMA has shifted from a progressive and quickly fatal disease to a treatable and now chronic disease. There are three approved products using different therapeutic platforms and routes of administration: intrathecal antisense oligonucleotide (ASO) nusinersen, intravenous AAV gene therapy onasemnogene abeparvovec, and the oral splicing modulator risdiplam.[8,9,10] These treatments have significantly improved survival and quality of life, while allowing paediatric patients to attain developmental milestones. Other important successes are the intrathecal ASO tofersen for amyotrophic lateral sclerosis with SOD1 mutations, the intraparenchymal gene therapy eladocagene exuparvovec for AADC deficiency, and the ex-vivo gene therapy atidarsagene autotemcel for metachromatic leukodystrophy.[11, 12, 13]

These approvals share communalities, thought to have contributed to these accomplishments and be translated to other programs: objective case definition; well-defined and/or relatively homogeneous natural history; known molecular pathophysiology; rational association between the molecular mechanisms, the targeted systems and the IP mechanism of action; existence of a technically feasible route of administration guaranteeing appropriate IP exposure; and well-validated outcome measures, including biomarkers and clinical outcome assessments.

There has also been progress in more prevalent conditions like AD, with three anti-amyloid monoclonal antibodies recently approved[14,15,16]. While the overall uptake has been limited due to payer/prescriber concerns regarding their efficacy and safety profiles and cost, these approvals represent an important milestone that motivates the pursuit of new interventions.

HISTORIC DEVELOPMENTAL LANDSCAPE

With high development risk, it is often difficult to justify the investment needed to bring these interventions to market. Historically, late development has been done in big pharma because of costs and the needed structure. However, recent approvals and regulatory flexibility have enticed unusual stakeholders. For example, regulatory authorities are willing to expedite the regulatory process where justifiable and encourage early engagement to discuss CMC and preclinical data, development plans, required clinical packages, expectations for study design, sample sizes, and outcomes. Overall, early engagement reduces uncertainty and promotes efficiency, making this space more appealing to less established companies and resource-constraint environments.

KEY STRATEGIES TO ACCELERATE ALZHEIMER'S AND NEURODEGENERATIVE TRIALS

To conduct clinical trials effectively and successfully in this space, partnering with a CRO that has relevant operational, regulatory and medical experience is an important de-risking strategy. A seasoned but flexible partner can offer invaluable insights gained from managing similar trials, including lessons learned in comparable indications, trial designs, regulatory and site interactions, and endpoint protection. Early engagement can streamline interactions with other stakeholders, such as regulators, ethics/IRB and sites, ensuring a seamless operationalization of the protocol.

Feasibility & Site Selection

There are key considerations specific to neurodegenerative trials during synopsis and protocol development. These have to do with study design (see Case Study 1) and procedures, such as biofluid collection and safety assessments, but also regulatory expectations and precedent, site and participant acceptability, and legal requirements around consent and capacity. Medical writing plays a crucial role in preventing sequential protocol amendments and delays, while selecting language that will be homogenously interpretated irrespectively of cultural and regional background.

> Case Study 1: An early-stage biotech company developed a protocol synopsis for their first-in-human study. Their partner noted that regional regulators have previously expressed preferences for dissimilar designs for the planed route of administration and therapeutic platform. A pre-emptive strategy was developed to appeal to all concerned authorities prior to protocol submission avoiding partial holds.

Recruitment can be challenging in these trials due to the rarity of some conditions, the need for study partner and/or legal authorized representatives, and participant burden (see Case Study 2). Nonetheless, there tends to be a positive attitude towards participation in neurodegenerative trials.

Site selection is likely one of the most important strategies for timely recruitment and study quality. As clinical care in neurodegeneration is often centralized, clinical referral sites are also research sites with veteran investigators and diligent research staff. Ensuring the selection of sites who are part of research networks, with known opinion leaders, and staff is trained on study procedures and assessments is almost always advantageous. Importantly, they may be overutilized and/or under resourced. While requiring more support and training, less experienced and even study-naïve sites can also be good recruiters, delivering timely and quality data as they are driven by the motivation to be involved and have available resources.

Recruitment & Retention

The hub-and-spoke model can be used to tap into populations that might not be seen in a reference centre but are suitable for the trial. For example, potentially eligible participants living in underserved areas can still participate in the trial. Solutions for participants in these areas include home health, using disease agnostic commercial sites, supporting participants to relocate temporarily to the main site or satellite site, and providing travel and accommodation support throughout the study.

In indications with multiple studies competing for a limited pool of participants, raising awareness through advocacy groups and digital advertising is an important recruitment tool. Patient organizations and advocacy groups play a vital role in creating awareness when there is a high unmet need. They serve as a point of contact for patients and often provide psychosocial care and support, in addition to the disease management provided by specialist teams. They are an invaluable resource that can bring the patient voice and perspective to clinicians, Sponsors and regulators at several stages of the program. Given their firsthand experience with the condition, connections with patients and the trust they have established, they can help manage patient expectations with the Sponsor to ensure successful recruitment and retention. While Sponsors often engage with opinion leaders when validating clinical development plans and protocols, service users input is sometimes overlooked: are clinical outcome assessment relevant, is the schedule of assessment burden justifiable, and are the potential risks acceptable? Some regulators now require this input as part of the submission process to promote early engagement.

Case Study 2: A recently launched company was developing an asset for a hyper-rare indication with less than 1,000 patients globally. A multimodal approach was implemented for recruitment: engagement with KOL/reference centres/research networks/participant organizations; hub-and-spoke site model; short and long-term traveling and accommodation support for domestic and international participants; social medical and traditional media engagement plan; community education initiatives. Recruitment completed on time with several potential participants directly approaching the Sponsor and partners.

Capacity & Consent

Capacity is a crucial concept in clinical research for these populations, particularly in relation to informed consent. For a study participant to validly consent to participating in a trial, they must be able to understand, retain and weigh the information of the study to make a decision and communicate their decision to the investigator. It is important to have a standardised consent process that are patient friendly and can be operationalised by sites. The consent process can be complex and should not be a 'one-size-fits-all' situation. The varying levels of capacity impact consent materials and consent process – there should be consideration for loss of capacity during a study and consent for a legal appointed representative (see Case Study 3).

Case Study 3: A platform company developed an asset for a global study for adults with impaired capacity. A rigorous site and patient friendly, country specific consent process was developed and implemented. The consent process considered not only regulatory requirements to obtaining consent in adults with impaired capacity (LAR consent/assent), but also capacity assessments specific to the study and study procedures, tailored site training for administration of capacity assessments and consent taking and study population and LAR appropriate consent materials including visuals, such as a video to aid understanding and communication of decisions.

Endpoint Protection

Data quality and outcome protection are key considerations during the development of study plans, study systems, and the integration between them to optimise study quality before and after enrolment. For example, to ensure successful randomisation, the study systems should be designed to support investigators in making suitable decisions (e.g., eCOA/IRT/CDR cross-talk and IRT edit-checks). After randomisation, it is essential to ensure the study systems captured all information required to answer the study questions and produce an informative clinical study report. One strategy to prevent missing information is working with an experienced CRO partner that can translate their experience. Worth considering is also, that people with dementia may struggle with study visits consisting of a full day of assessments or interactions with many different people. To mitigate this, establishing a set order of assessments and consistency in site staff can help manage the patients' expectations and improve assessment completion and overall retention.

It is important to ensure there is an understanding of how assessment tools behave in certain populations when measuring effects, whether a clinical, biochemical or imaging effect. Additionally, it is essential that the tools are well-validated and accepted by the regulators in terms of reliability and usefulness. Endpoints and outcome measures can be particular in neurodegeneration, namely clinical outcome assessments, biomarkers and safety assessments. For example, it is expected that suicidality is captured with tools such as the Columbia Suicidality Severity Rating Scale (C-SSRS) from screening to end of study.

Finally, study results require contextualization, which can be difficult without prior knowledge and experience dealing with the participant population. Internal experience and opinion leaders are typically relied upon for interpretation; however, contextual aspects of running the study that are crucial may be lost, such as recruitment, retention, amendments and protocol deviations. Expert support can ensure no important information is missed from the clinical study report.

CONCLUSION

AD and neurodegenerative diseases are at the forefront of clinical research and there is a large unmet need for new treatment options due to the complexities involved. Recent breakthroughs showcase the power of innovation, collaboration and early engagement between Sponsors, CROs, sites, regulators, advocacy groups, opinion leaders and patients. Looking ahead, the field of neuroscience holds immense promise for improving the lives of those with neurodegenerative diseases, including AD.

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