Worldwide Clinical Trials

Transforming Neurodegeneration Trials: Strategic Decisions in Clinical Development Planning Involving Biomarkers and Precision Medicine

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Abstract

Neurodegenerative disease (NDD) clinical trials face significant challenges due to patient heterogeneity in clinical presentation and progression rate, all of which require centrally acting therapies that must pass the blood-brain barrier and precisely engage with the target to prevent off-target effects. Biomarkers, including fluid, digital, and imaging-based, enable patient stratification, facilitate early diagnosis, and serve as predictive and pharmacodynamic indicators of treatment response. Enrichment strategies, while enhancing signal detection, introduce trade-offs between sample size, translatability, and enrollment speed. Prognostic modeling, powered by machine learning, refines patient selection and improves trial design by integrating genetic, molecular, and clinical indicators. As regulatory expectations change, biomarker validation and standardization are critical for their acceptance as potential participant selection criteria or clinical endpoints. Successful biomarker-driven trials require strategic selection of capable and experienced sites, robust sample handling logistics, and collaboration with patient advocacy groups (PAGs) to optimize recruitment and retention. NDD trials hinge on continued advancements in biomarker science, enhanced prognostic modeling with AI-driven analytics, and global research collaboration to facilitate earlier interventions and more personalized treatment strategies. This white paper explores in-depth biomarkers and precision medicine strategies that can improve trial efficiency and therapeutic outcomes.

Introduction

Neurodegenerative diseases (NDDs) are among the most challenging conditions in modern healthcare, with clinical trials often facing significant hurdles that can delay progress and hinder the discovery of new treatments. NDDs are characterized by the progressive degeneration of the structure and function of the nervous system, making them complex to diagnose and treat. One of the primary challenges in advancing NDD research is the significant patient heterogeneity across and within diseases, where patients present with a wide range of symptoms and disease progression rates, making it challenging to develop and test universal treatments and ensure early intervention.[1]

To address this complexity, pairing the right patient with the best-matched treatment is essential for optimizing clinical outcomes and overall trial success. However, it is inherently complex due to the diverse pathophysiology of neurodegenerative conditions. Biomarkers, including fluid-, image- and digital-based, are emerging as promising molecular indicators that can help identify specific subtypes of diseases, predict disease progression, and monitor therapeutic efficacy.[2] Biomarkers represent a method that allows researchers to increase the study's ability to detect or confirm a pharmacodynamic effect, either as a precise measure or employ given biomarkers to segment the overall population, as the foundation of an enrichment strategy intended to improve the signal to noise ratio and thus increase the probability of detecting a therapeutic effect.

> Biomarkers represent an emerging opportunity to pair the right patient with the best-matched treatment.

A strategic recruitment approach is essential because traditional patient recruitment methods often fail to account for the nuanced differences among patients, leading to less reliable trial results and requiring advanced methodologies and creativity to identify and enroll patients most suitable for specific trials. Precision medicine customizes treatments for each patient using genetic, molecular, and phenotypic data to match them with the most effective therapy for better outcomes.[3] By combining biomarkers with innovative design and operation techniques, researchers are improving the success rates of clinical trials and accelerating the development of new and more effective treatments for NDDs.

Multifaceted Role for Biomarkers within NDD Clinical Trials

Several types of biomarkers, whether fluid, imaging, or digital, are currently under development and validation for use within the main NDD indications.[4-6] Biomarkers have utility across the clinical trial course, from participant identification to treatment response and overall outcomes. They broadly fall into several categories: diagnostic, prognostic, predictive, pharmacodynamic response, and safety (Figure 1).

Diagnostic biomarkers identify individuals that qualify as having a specific NDD based on essential biomarkers such as amyloid beta (Aβ) or tau levels in cerebrospinal fluid (CSF) and more recently also in serum, as well as on neuroimaging for Alzheimer's disease (AD).[7] Similarly, prognostic biomarkers indicate likely disease course independent of treatment, such as NfL as a marker of neuronal damage in amyotrophic lateral sclerosis (ALS) or multiple schlerosis (MS).[8,9] For patient identification, predictive biomarkers help identify those more likely to respond positively to a treatment, which contributes to more strategic and effective enrollment and overall likelihood of successful study outcomes. When investigating a novel interventional therapeutic or pharmacodynamic response, biomarkers help measure treatment response to guide dose optimization and contribute to patient safety. Biomarkers thus often serve as a safety monitor to indicate potential adverse effects during therapy, such as monitoring inflammatory markers during gene therapy, to detect immune responses. Also, biomarkers, including CSF or PET scans, have been postulated as potentially valuable for predicting amyloid-related imaging abnormalities in AD treatment with anti-Aβ antibodies.

Entry Criteria and Enrichment Strategy

It is often vital to control for disease heterogeneity in NDD research, where enrichment strategies define a more homogenous sub-population, which can enhance the possibility of signal detection by minimizing the variance within the clinical assessment data across the analysis. Factors used to segment the population in this manner are carefully selected based on the endpoint, timeframe, and biological motif. Trials may achieve this by studying within a specific clinical phenotype or genotype or applying thresholds to biomarkers. Innovative recruitment strategies involving advanced data analytics and patient registries can help overcome challenges and ensure that clinical trials are more representative and effective (Table 1).[10] Challenges exist when using very tight population

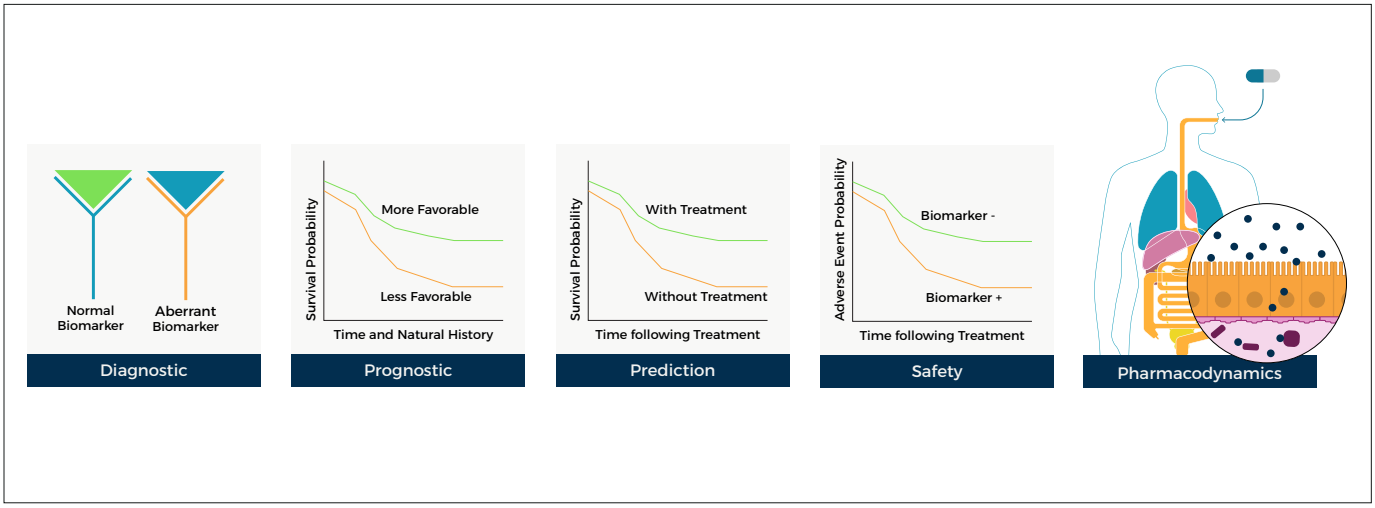

Figure 1. *Biomarkers display utility across the clinical spectrum.*

controls, such as a genetic variant or biomarker-based enrichment strategy, including the following:

1. Translatability of results in a specific population versus the all-comer population (i.e., the restriction applied to target product claims and the sub-population impacts the label granted at marketing authorization approval)
2. Risk of development strategy becoming wedded to developing and marketing a companion diagnostic

Using an enrichment procedure creates a paradox. Enrichment strategies imply a slower enrolment rate and a smaller sample size but greater endpoint precision. Conversely, broader trials display more heterogeneity and inherent variability in the data, requiring larger sample sizes to overcome this hurdle.

Table 1: Example natural history studies and longitudinal registries of genetic forms of select NDDS

Condition	Registry	Biomarkers
GBA Parkinson's Disease	University College London Registry	Glucocerebrosidase (GBA) gene
Frontotemporal Dementia	GENFI Organization	Progranulin (PGRN) gene MAPT gene C9orf72 gene

Conditions in which patient registries exist facilitate streamlined participant identification of likely eligible and interested participants.

Trials can counter this by achieving faster enrolment rates because of fewer eligibility restrictions. If taking the enrichment pathway for enrollment, one strategy could involve limiting to a genetic form of disease relevant to the mode of action. Another could be a proof of concept (POC) study in a specific genetic variant because it has improved translational value over the all-comer population and a more homogenous progression rate or more similar clinical phenotype (e.g., GBA Parkinsons, SOD1-ALS, or APoE4 AD).

Trials may also extend this enrichment to define specific study populations with early-stage disease and adequate pathophysiology that a therapeutic can target. For example, combining pTau, tau PET imaging, disease staging, and clinical outcomes assessments can define early AD or mild cognitive impairment (Table 2).

Stratification

Where a biomarker is known to correlate to disease progression or represent a risk to successful outcomes, it may be used as a stratification factor to minimize unintended bias, where it prevents the unequal distribution of people with the biomarker of interest between the studied interventions at the time of randomization.[10] For example, the Biogen ATLAS trial, NCT04856982, is enrolling pre-symptomatic SOD1 variant carriers to commence tofersen treatment prior to ALS phenoconversion, based upon reaching a pre-determined NfL threshold (AHEAD; registry number: NCT04468659).

Stratification also plays a vital role within the study cohorts. To avoid inadvertent bias or statistical errors,

Table 2: Current seminal trials in pre-symptomatic patients

Condition	Registry	Biomarkers
ALS	ATLAS	SOD1 carriers can join when NfL reaches pre-defined threshold and can start Tofersen/Qalsody
Alzheimer's Disease (AD)	Biogen/Eisai AHEAD	Pre-symptomatic AD patients can start lecanemab (Leqembi)

Both ALS and AD have seminal trials that study pre-symptomatic patients with specific biomarker signatures, intervening before the NDD becomes clinically manifested through phenoconversion.

equally distribute participants by biomarker status within intervention groups (treatment arms). For example, for NDD studies involving neuronal damage, such as ALS or MS, baseline NfL levels used as stratification factors or covariates within the analysis modeled outcomes may help to minimize unintended bias between groups.

Prognostic Modeling

Prognostic modeling for NDDs combines various biomarkers and clinical indicators, including genetic influences, into a comprehensive framework. These models provide a detailed view of a patient's condition by integrating data from imaging results, blood-based biomarkers, and genetic profiles.[11] This holistic approach is essential for understanding the neurodegeneration mechanisms, as it captures visible clinical signs and subtle biological signals that trials and clinicians might otherwise miss (Figure 2). The practical benefits of prognostic modeling can serve as a key factor in enrichment, stratifying patients, or analyzing covariates.[12]

Machine learning (ML) techniques significantly improve the predictive power of these models. ML algorithms can analyze large and complex datasets to identify patterns correlating with disease progression, turning raw clinical data into useful information.[13] These data help detect rapid deterioration early and deepen our understanding of how different biomarkers interact over time. As a result, clinicians can predict the disease course more accurately, leading to timely interventions and personalized treatment strategies tailored to each patient's unique risk profile. A prognostic model can serve as a single stratification factor, considering multiple prognostic aspects. This makes effective prognostic modeling superior to applying multiple strata for each prognostic or risk factor, which results in numerous small groups of patients within each stratum, thus reducing the power of analysis. Beyond that, patient avatars (i.e., synthetic controls) minimize placebo groups, effectively reducing the number of required study participants, increasing the enrollment speed, reducing the number of sites needed, and ensuring that most enrolled participants gain access to the active treatment. Incorporating patient avatars into protocols can reduce the total cost while increasing the statistical power. However, regulatory acceptance of these approaches is an evolving area.

Additional uses could help in providing counseling. By categorizing patients into distinct subgroups based on their biomarker profiles and progression risks, healthcare providers can create more effective treatment plans. This categorization ensures that each patient receives the most suitable care for their condition. Furthermore, these insights help facilitate informed discussions with patients and their families, giving them a clearer understanding of the disease's trajectory.

Biomarkers as Primary and Key Secondary Clinical Endpoints

Some biomarker signatures inform target engagement, others for POC with biological plausibility action within a specific pathway, the proposed pathology hypothesis, or as a measure of POC for a biomarker validated against a clinical endpoint that measures severity or progression rate. However, detecting clinically relevant differences requires an extended timeline and is not always feasible in a standard

Figure 2. *Prognostic modeling involves multiple combinatory approaches to ensure the correct participant demographic and improve the likelihood of intervention success. Often, trials can combine biomarkers with clinical assessments of disease progression based on validated scales and perform noninvasive imaging to identify optimal candidates.*

trial. Similarly, the clinicopathologic correlation for biomarkers entails demonstrating that a biomarker reflects a key disease mechanism and that its modulation correlates with clinical benefits.[2] In the context of NDDs, this involves showing close ties between the biomarker and the disease process and that changes in the biomarker, whether through natural progression or therapeutic intervention, predict meaningful clinical outcomes. Establishing clinicopathologic correlation starts with demonstrating a mechanistic connection between the biomarker and the disease process. For instance, increased pTau is a hallmark of Alzheimer's pathology. Studies must show proof that a therapeutic intervention can alter the biomarker. Trials might show this via preclinical studies using animal models or Phase I human trials where treatment leads to measurable changes in the biomarker. Crucially, any change in the biomarker should predict or correlate with clinical endpoints, such as improvements in cognitive function or slowing disease progression. The heterogeneous nature of NDDs requires careful consideration, as reproducibility may pose challenges.

Fluid biomarkers hold potential as key measures used within drug development strategy to expedite marketing authorization approval. With favorable data, a fluid biomarker that is pre-determined to be validated against the regulatory acceptable clinical outcomes assessment and hence reasonably likely to predict the clinical outcomes when used over a shorter time course may serve as the principal evidence in accelerated approval. For instance, the FDA guidance for the biomarker qualification process underscores the importance of the Clinical Path Initiative (CPI). The CPI identifies and prioritizes potential drugs, biological products, or medical devices as they transition from discovery to public availability. Biomarkers, as objectively measured agents, evaluated to indicate biological processes, including typical, pathogenic, or treatment response-based readouts, when appropriately utilized, can position a new therapy for expedited approval, often including patient-reported outcomes, as well.[14]

Biological POC for an NDD biomarker is the process of confirming that:

- The biomarker accurately reflects a core aspect of the disease biology
- It responds in a predictable manner to therapeutic interventions
- Its changes are reliably associated with meaningful clinical improvements

A typical utility would be in a seamless Phase II/III trial where a biomarker readout conduction occurs over a short time as Phase II of development. The study continues into an extended treatment period, which constitutes Phase III, and uses a clinical outcomes assessment. For example, this has successfully been deployed in SOD1-ALS using NfL in the short term and ALSFRS-R over a more extended period. Similarly, as seen in AD, the FDA approved Leqembi based on clinical efficacy using amyloid PET as a surrogate biomarker, owing to its consistent agreement with other clinical outcome measures and biomarkers.[15]

Biomarkers as Central Components for Development Strategy

The development strategy process is quite nuanced and filled with many possibilities depending on the goal, as illustrated in the context of the clinical development strategy in using NfL as a biomarker for ALS (Figure 3). With that in mind, it is increasingly likely that biomarkers will be a critical component of the development strategy for investigational products intended as disease-modifying therapies of NDDs, and the biomarker uses described above have implications on classical project constraints such as timelines, cost, and quality. Additionally, increasing interdependencies must be managed due to more preclinical and clinical activities by specialist service providers. Studies must build the pivotal role of biomarkers, the activities required to ensure the adequacy of their validation status, and their regulatory acceptance into the clinical development plan timelines and strategic and regulatory documentation.

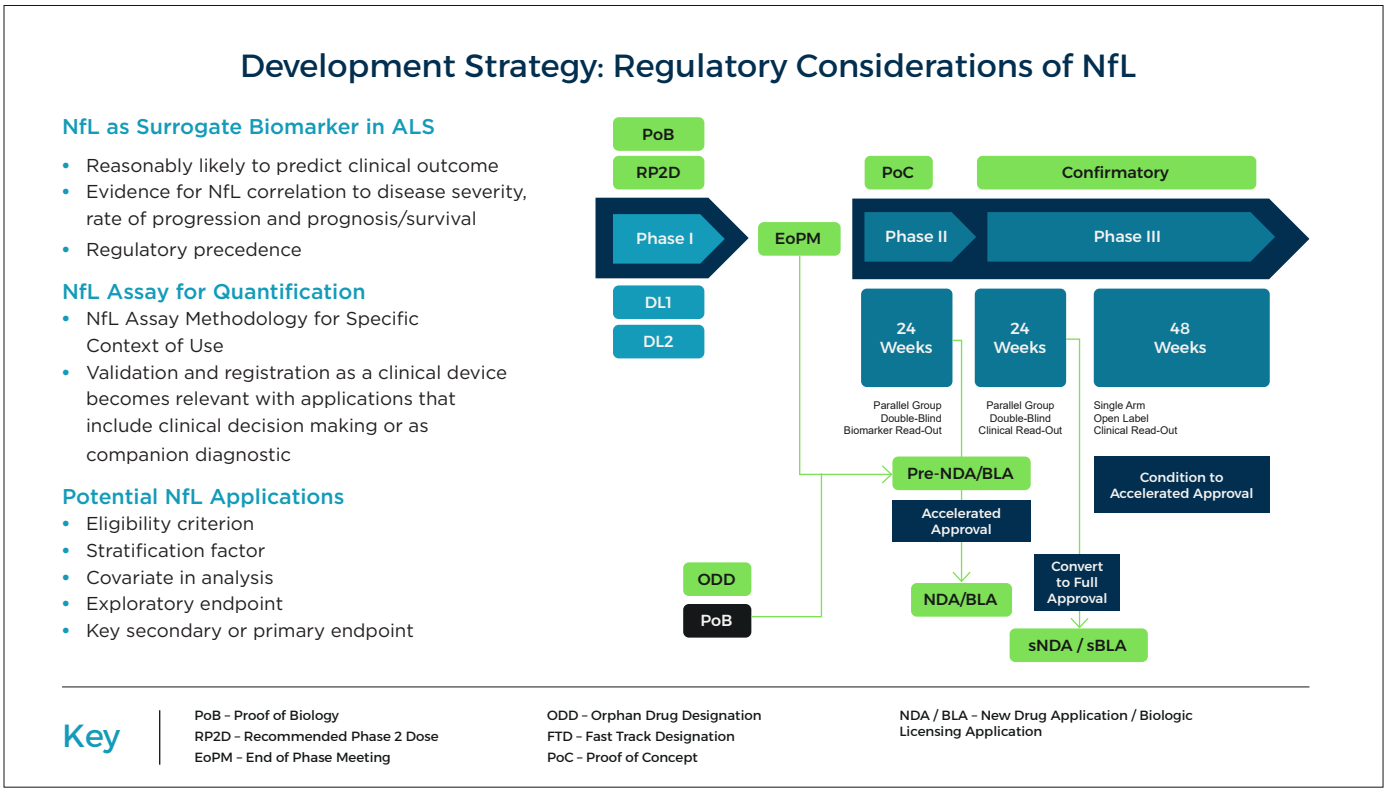

Figure 3. *Development strategy pathway for using NfL in an ALS clinical trial.*

Regulatory Considerations: Context of Use

The appropriate level of validation required for a biomarker depends on its intended context of use. Essentially, this is either exploratory use or use for clinical decision-making. Exploratory uses include exploratory endpoints, covariates in analysis, or stratification factors, whereas clinical decision-making uses include diagnosis, eligibility, and primary or secondary outcome reporting. This means extensive evidence is required to demonstrate that the biomarker is analytically reliable and clinically relevant. Regulators will look for data that shows a strong correlation between changes in the biomarker and meaningful clinical outcomes, ensuring that the biomarker accurately captures the effect of the intervention on disease progression.[16] In this context, assay standardization, reproducibility, sensitivity, and specificity are critical, and the biomarker must directly link its modulation to patient benefit, with many biomarkers currently as candidates for use in various NDDs.[2] A regulatory strategy should thus include increased competent authority interactions with scientific advice intended to understand the acceptance of the proposed biomarkers, in principle, for the specific strategic uses described.[17]

Aligned with this strategy, the FDA recently accepted the Biomarkers Consortium letter of intent to qualify FTD biomarker that was part of the output of an FNIH project, "Neurofilament as a Fluid Biomarker of Neurodegeneration in Familial FTD," as there was a sound body of evidence that points towards NfL rise in people carriers of risk-creating mutations of GRN or MAPT genes well before symptom onset.

Certain biomarkers may complement the primary endpoint for secondary analyses by providing supportive evidence or mechanistic insights. This use-case is relevant when the primary endpoint is typically a clinical outcome assessment; a biomarker may provide supportive mechanistic evidence as a lower-ranking endpoint. Although the validation requirements are generally less demanding than those for primary endpoints, regulators expect these biomarkers to be measured reliably and consistently across the

Trials must comply with CLIA, IDEs, and IVDR to satisfy regulatory expectations for a biomarker. In the E.U., commercial testing kits are required to carry a CE mark.

study population. Clear pre-specification in the study protocol is essential, along with evidence that these biomarkers can enhance the interpretation of the primary outcome data.[17] In this role, the biomarkers can help explain variability in patient responses or uncover additional dimensions of the disease process, but they are not the sole basis for efficacy claims.

When researchers use biomarkers in an exploratory capacity, the regulatory expectations are more flexible. Exploratory biomarkers are often included in early-phase studies or as part of a broader effort to understand disease biology. While full registration is not mandatory in these cases, there must be a well-articulated rationale for their inclusion and transparently reported methods used to assess them.[18]

Biomarkers, whether used as evidence of target engagement, evidence of disease modification, diagnostic tools, entry or enrichment criteria, or tools to minimize unintended bias such as stratification factors or covariates, their role in clinical development strategy continues to be elevated by basic research breakthroughs and contribute to more rational study designs based on biological plausibility.

Operational Implications

Biomarker-based assessment requires exact operations, carefully mapped out to ensure the trial design covers sample collection, transport, storage, and analysis to ensure validity between samples over time. In addition, protocols must consider the overall trial timeline, make careful decisions on when to collect samples for analysis and ensure radiolabeling and isotope availability close to active sites. Beyond this, the protocol must include pre-defined safety monitoring plans for in-patient and at-home components.

When selecting service providers, from operational implications, it is essential to strategically select the country and sites, which may need to consider access to supplies and consumables and validation status of biomarkers (e.g., requisite CE marking required for E.U. for companion diagnostics). At a granular level, it is critical to select vendors that operate at the necessary capacity, with a historic reputation of on-time and on-budget delivery, and establish a transparent performance management system to guarantee any potential issues, whether related to the study timeline or regulatory implications, are addressed as soon as possible, or escalated as needed.

Performing trial readiness activities, such as biomarker identification, validation, and access to a natural history registry, is helpful. At the screening and recruitment stage, it is wise to prepare for additional complexity in the participant screening process and eligibility review; this could include a tiered screening approach to identify screen failures at the lowest burden, strain, and investment (i.e., CoA, fluid, or imaging). Participant identification and recruitment may require collaborations with consortia or non-profit organizations, making it noteworthy to engage with these organizations early and often to develop a good rapport and increase participant awareness. When establishing participant and caregiver information and consent materials, the best outcomes result from including complex themes in lay language so that everyone involved knows what they can expect from the trial.

During testing, protocols should plan for extended screening periods for returned readouts, which requires a delicate balance, as trials often require testing in real time unless analysis is deferred until the end of the trial to reduce variability or maximize laboratory efficiency. Regardless, trials must prepare for adequate timing for regulatory strategy and scientific advice meetings to discuss concepts such as population definition, analysis definition or endpoints, and acceptance as surrogate markers to best position their research for acceptance.

The variability in biomarker assays can complicate clinical trial integration, highlighting the need for regulatory harmonization and validated assay

development. Longitudinal data become another hurdle when designing the study, as the progressive nature of NDDs requires long-term biomarker data to track the disease and treatment effects over time. It can be complicated to retain participant engagement, and there is a high mortality associated with many NDDs. Moreover, some biomarkers may not carry approval across different regulatory bodies, further complicating matters. For example, combining PET imaging and pTAU217 biomarkers does not have the requisite CE mark for trials conducted in the E.U.

Choosing the right site locations with adequate capabilities specific to NDDs can significantly impact the success and efficacy of the trial. For example, as NDDs involve significant motor issues that create patient accessibility complications, sites must have the capacity for handling these issues, including ramps, sufficient handles and guide rails, and an overall patient-friendly environment. The proximity to essential supplies, services, and validated tests is equally crucial for the smooth operation of an NDD clinical trial. Considerations include:

- Access to a reliable supply chain for all relevant sample processing components
- Physical proximity to high-quality laboratories to ensure rapid, accurate, and consistent readouts
- Availability of supplies for validated tests, as some reagents are more challenging to secure and, if not properly planned, could lead to significant delays in the trial timeline and reduced chances of trial success

Imaging or digital biomarkers may require that necessary equipment be provided to participating sites to ensure uniformity. Additionally, centralized reading or analysis may be necessary, typically requiring the engagement of specialized service providers (i.e., vendors) whose delivery must be coordinated within the context of participant clinical visits and data analysis needs. For example, actigraphy within PD or speech analysis within ALS will require specific devices or apps with the support of back-end analytics.

More specific entry criteria based on a biomarker may foster a closer relationship between PAGs, consortia, and academic or non-profit projects since cross-sectional or longitudinal natural history data from patient registries or biorepositories may supplement study enrolment or biomarker identification and validation.[19] PAGs and non-profits often go through a "trial-ready" process for a specific patient population, often in rare diseases, where they identify candidate biomarkers and establish natural history. Illustrating this point, in the FTD field, the efforts of GENFI will allow for trial readiness, with natural history databases of genetic forms of FTD having the potential to supplement efforts with biomarker validation.

Biomarker assay variability further highlights the need for regulatory harmonization.

Future Directions

Breakthroughs in basic science will lead to more markers emerging as correlational studies come out between potential biomarkers and observed clinical outcomes. By integrating advanced fluid and imaging biomarkers with digital health technologies and leveraging AI-driven data analysis, researchers create more personalized and effective interventions for neurodegenerative disorders. Regulatory bodies will conceivably accept surrogate endpoints that are reasonably likely to predict clinical outcomes based on leading candidate biomarkers for disease progression for each NDD and status, contingent upon increased scientific evidence. Advancements in neuroimaging techniques and growing acceptance of integrative approaches that could include fluid and genetic biomarkers alongside imaging can improve diagnostic accuracy and patient stratification holistically.

As a result of these advancements and evolving sentiments, there will likely be an increase in validated biomarkers in the clinical decision-making context of use by more service providers. This will complement an increased collection of biomarkers within longitudinal patient registries, facilitating clinical trial enrollment and forming a cyclical and mutually progressive cadence. There is likely to be an increased use of biomarkers in routine clinical practice that will facilitate more accurate precision medicine, leading to earlier intervention, greater identification of patients for clinical trials, and increased probability of treatment efficacy. In the big picture, researchers can intervene more effectively by identifying molecular signatures early, potentially slowing or halting disease progression and improving patient outcomes.

Appendix I: Current biomarkers of interest across NDDs

Disease	Blood-Based	Cerebrospinal Fluid	Imaging	Digital	Genetic
Alzheimer's disease (AD)	• p-tau (181, 217, 231) • Amyloid-β • NfL	• p-tau (181, 217, 231) • Amyloid-β • NfL	• A-PET • FDG-PET • MRI atrophy		• PSEN1 • PSEN2 • ApoE4/4
Dementia with Lewy bodies (DLB)	• NfL	• NfL	• DaTScan Perfusion • SPECT • FDGPET • PSG-RBD		
Progressive supranuclear palsy (PSP)	• NfL • GFAP	• NfL • GFAP • ATP6AP2	• MRPI • AID-P		
Frontotemporal dementia (FTD)	• NfL • TDP-43 • PGRN • miRNA	• NfL • t-tau • TDP-43 • p-tau/t-tau miRNA • Angiogenin • Neuronal pentraxin	• MEG – FL/PL atrophy		• C9orf72 • MAPT • GRN • VCP • CHMP2B • TARDP • FUS
Parkinson's disease (PD)	• α-syn-SAA • IL-6 • TNF-α • IL-1β • CRP • CCL2	• α-synuclein	• DaTSpec • Neuromelanin sensitive MRI • Iron sensitive MRI • Cardiac MIBG	• Tremor • Bradykinesia • Gait	• GBA1 • LRRK2
Huntington's disease (HD)	• NfL	• mHTT	• MRI – caudatus atrophy	• Gait • Chorea	• CAG > 36(39)
Multiple sclerosis (MS)	• NfL • GFAP	• NfL • OCB • GFAB	• MRI T1 vs. T2 • OCT • VEP • MRI – atrophy	• Gait	
Multiple system atrophy (MSA)	• NfL • GFAP	• NfL	• MRI – Putaminal slit		
Amylotrophic lateral sclerosis (ALS)	• NfL • pNfH/NfH	• NfL			• SOD1 • C9orf72

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