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INVITED COMMENTARY

Clinically meaningful benefit and real-world evidence in Alzheimer's disease research and care

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Abstract

In the realm of medical research, assessing novel therapies extends beyond statistical significance. The concept of meaningful benefits plays a pivotal role in determining the practical impact of interventions on patient outcomes. Clinical trials, which form the bedrock of evidence-based medicine, guide treatment decisions and shape healthcare practices. While statistical significance remains a fundamental criterion, it falls short in fully evaluating the clinical relevance of therapeutic interventions. Clinically meaningful benefits focus on tangible improvements in patient health and well-being, transcending mere statistical thresholds. Key considerations include survival rates, symptom relief, functional status, and other patient-oriented outcomes. Determining meaningful benefits varies across diseases, patient populations, and available treatments. Balancing statistical rigor with clinical relevance is crucial. Overpowered trials may detect smaller differences than anticipated, necessitating careful interpretation. Researchers must view trial results through a patient-centric lens. Beyond survival, evaluating quality of life and side effects is equally relevant. Quantifying meaningful benefits involves metrics like numbers needed to treat and progression-free survival. Consistency across outcomes matters, as clinicians weigh gains in survival against improvements in quality of life. The pursuit of meaningful benefits elevates clinical trials from mere statistical exercises to patient-centered endeavors. Researchers, clinicians, and regulators must prioritize outcomes that genuinely matter to patients, ensuring that medical progress translates into meaningful improvements for them and their families.

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Alzheimer's disease and neurodegeneration, biomarker-based early and accurate diagnosis, disease prevention and early intervention, disease-modifying and symptomatic treatment, mild cognitive impairment and dementia, patient autonomy and independence

1 | THE CONCEPT OF CLINICALLY MEANINGFUL BENEFITS

In medical research, the evaluation of novel therapies extends beyond mere statistical significance. The concept of meaningful benefits plays a pivotal role in determining the practical impact of interventions on patient outcomes.[1] This article explores the nuances of assessing meaningful benefits, emphasizing their relevance in clinical trial design, interpretation, and patient-centric decision making. Clinical trials serve as the foundation for evidence-based medicine, guiding treatment decisions and shaping health-care practices. While statistical significance remains a fundamental criterion, it is insufficient to fully assess the clinical relevance of a therapeutic intervention. Different frameworks to measure clinically meaningful benefits aim to bridge this gap by emphasizing the need for tangible improvements in patient health and well-being (Table 1).

Clinically meaningful benefits in Alzheimer's disease (AD) research refer to outcomes that have a tangible impact on patients' daily lives and overall well-being. Unlike statistical significance, which indicates a measurable change in clinical trial data, clinically meaningful benefits are anchored to changes that clinicians, patients, and caregivers perceive as valuable and/or are correlated to changes in patient-reported outcome measures (PROMs) or patient-related experience measures (PREMs). For example, a statistically significant improvement in cognitive function tests is often anchored to statistically significant changes on standard cognitive/functional composites reflecting the natural course of the disease, thus highlighting the extent of "rescuing" of decline needed to demonstrate meaningful benefit. Another example is to translate significant improvement in cognitive function tests into noticeable enhancements in daily activities and quality of life to be considered clinically meaningful. This distinction ensures that the benefits observed in clinical trials are relevant and impactful for those living with AD.

The concept of clinically meaningful benefits in AD research has been explored in recent literature. For instance, the expectations and clinical meaningfulness of randomized controlled trials were discussed, highlighting the importance of aligning trial outcomes with patient and caregiver priorities.[2] Similarly, a qualitative study to assess what matters most to patients with or at risk for AD and their care partners emphasized the significance of symptoms, impacts, and outcomes that resonate with these groups.[3]

The magnitude of a treatment effect matters and the concept of clinically meaningful benefits refers to the smallest effect size that holds clinical significance. It transcends statistical thresholds and focuses on outcomes that make a difference to patients, caregivers, and health-care providers. Key considerations include survival, symptom relief, functional status, and other patient-oriented outcomes. The determination of meaningful benefits varies across diseases (and disease stages), patient populations, and available treatments. For instance, in oncology, the American Society of Clinical Oncology recommends a 20% relative improvement in overall survival as a clinically meaningful threshold.[4] However, context is key, and a 20% improvement may be substantial in advanced cancer but less impactful in early-stage disease.[5]

Balancing statistical rigor and clinical relevance is also important, and clinical trials are designed with hypothesized effect sizes. Overpowered trials may detect smaller differences than anticipated, necessitating careful interpretation.[6] Researchers must strike a balance between statistical rigor and practical significance, interpreting trial results with a patient-centric perspective.

The objective effectiveness of a drug is an important measure for its clinical value for obvious reasons, but quality of life and side effects are equally relevant.[7] The evaluation of meaningful benefits extends beyond mere survival and delayed progression of symptoms. Quality of life maintenance or gains, longer disease control, and other qualitative measures related to the lower burden of disease, for example, numbers needed to treat and progression-free survival, indicate clinical benefit. Clinicians must weigh gains in survival and clinical decline against beneficial effects on quality of life. The pursuit of meaningful benefits elevates clinical trials from statistical exercises to patient-centered endeavors. Researchers, clinicians, and regulators must prioritize outcomes that truly matter to the patients, ensuring that medical progress translates into meaningful improvements for them and their families.[8]

2 | THE EVOLUTION OF MEANINGFUL BENEFITS IN AD RESEARCH

The modern era of drug development for AD began with the proposal of the cholinergic hypothesis of memory impairment[9] and the 1984 research criteria.[10] Key milestones from the last four decades related to evaluating AD treatments include the 1990 introduction by the US Food and Drug Administration (FDA) of a dual-outcome approach for clinical trials,[11] aligning with European Medicines Agency (EMA) standards. This approach involved two main assessments: (1) cognitive assessment, specifically the ADAS-Cog11 (11-item Alzheimer's Disease Assessment Scale-Cognitive subscale) was used; moreover, (2) a broader assessment of global functioning or activities of daily living was considered. These dual outcomes aimed to capture both cognitive deficits and their functional consequences in AD, and were intended to ensure treatment effects on cognition are clinically meaningful for patients and their caregivers.[12] These outcomes were primarily

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TABLE 1 Examples of different metrics for assessing clinically meaningful benefits in AD research.

Metric	Description	Pros	Cons
Cognitive function tests	Measures cognitive abilities such as memory, attention, and problem solving	Provides direct assessment of cognitive changes	May not fully capture functional or quality-of-life improvements
Functional assessments	Evaluates the ability to perform daily activities	Reflects real-world impact on daily living	Can be subjective and influenced by external factors
Patient-reported outcomes (PROs)	Self-reported measures of symptoms, quality of life, and overall well-being	Captures patient perspectives and experiences	Subject to reporting bias and variability
Caregiver-reported outcomes	Reports from caregivers on patient symptoms and caregiving burden	Provides insights into caregiver burden and patient autonomy	May be influenced by the caregiver's own stress and experiences
Biomarker-based assessments	Uses biological markers to assess disease progression and treatment effects	Objective and quantifiable measures	High cost, limited accessibility, and variability across populations
Time-to-event analyses	Measures the time until a specific event occurs, such as disease progression	Useful for assessing long-term outcomes and treatment durability	Requires long follow-up periods and may be influenced by external factors
Cost-effectiveness analyses	Compares the costs of treatments to their clinical benefits	Provides insights into the economic feasibility and value of treatments	Requires detailed cost data and may be complex to conduct

Abbreviation: AD, Alzheimer's disease.

applied in short-term clinical trials for cognitive enhancer treatments in mild-to-moderate and moderate-to-severe AD. The FDA mandated a 6-month clinical trial duration for assessing the effectiveness of cognitive enhancers, followed in 2013 by clinical trial advancements occurring with symptomatic treatments.[13] In 2016, both the FDA and EMA endorsed composite primary outcome measures for evaluating treatments, integrating assessments of cognitive and daily function, with the EMA providing guidance in 2018[14] on trials focusing on early AD and slowing disease progression, emphasizing the importance of meaningful benefits.[15] Time-to-event analyses to measure the ability of a disease-modifying therapy (DMT) to delay the occurrence of a pre-specified clinically meaningful event (such as progression to a more severe disease stage) is mentioned in the new FDA draft guidance as an acceptable primary efficacy measure in early AD clinical trials.[16]

Until recently, only two drug classes were approved for the treatment of AD dementia, with transient symptomatic effects only, based on modulating neurotransmitter function; cholinesterase inhibitors to improve cholinergic function and NMDA receptor antagonists to modulate glutamate activity.[17] However, the recent diversification of drug targets and the introduction of drugs with disease-modifying properties aiming to slow disease progression has important implications on how to capture the meaningfulness of treatment effects. Compared to the symptomatic treatments, these new drugs are currently intended for earlier AD stages (i.e., mild cognitive impairment [MCI] and mild dementia stage), in which clinical decline is less dynamic and more variable and during which symptoms are less impairing compared to more advanced disease. Even though trials for disease-modifying drugs are longer (18 months on average for the double-blind period), the observation period is still too short to effectively evaluate all long-term benefits of treatments that slow disease progression and clinical decline but do not improve symptoms. This mandates a more personalized approach to assessing meaningful treatment effects on an individual patient level. Regulatory agencies must evolve to accommodate innovative drug classes and personalized approaches.

To demonstrate meaningfulness, the observed placebo versus treatment differences must be contextualized under careful consideration of the key characteristics of AD. Although the initial symptoms are mild, progress only slowly, and are challenging to distinguish from normal aging, AD is a deadly disease with severe consequences for the affected individuals and their families, just like most cancers. Treatment effects are most relevant in the earliest stages (including disease prevention), when autonomy is still relatively preserved and positive consequences on quality of life are most likely. Upon longer observation, an additional meaningful benefit can arise, which during the trial period may only be evidenced by surrogate biomarkers and clinical endpoints (such as quality-of-life measures).

Multidimensional clinical outcome measures, beyond core symptomatic assessments of cognition and function, are required to fully capture clinical meaningfulness, including patient- and caregiver-reported outcomes, neuropsychiatric symptoms, and biological surrogate markers.[18] Simple numeric thresholds on single trial endpoints do not sufficiently capture these complex changes. Criteria that demonstrate meaningful benefit include changing the rate of disease decline (i.e., slowing the progression of symptoms on measures of cognition and function); if a treatment can slow down the progression of AD, it provides meaningful benefit. This can be demonstrated by an increasing drug–placebo difference in a clinical trial, for example, by slope analysis and other complementary analyses of clinical trial data, such as time-to-event (or time-saved) analysis; if the treatment extends the time before a significant event occurs (such as severe impairment), it is considered meaningful. Finally, surrogate biomarker changes predicting future clinical benefit may provide relevant insights; biomarkers

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that correlate with future clinical benefits may demonstrate meaningfulness. These criteria may guide the evaluation of potential treatments and their impact on patients' lives in real world data sets.

3 | DIFFERENT APPROACHES TO MEASURING MEANINGFUL BENEFITS

Common analyses used to determine meaningful benefits include minimum clinically important difference,[19] representing the smallest clinically detectable difference in an outcome that is considered meaningful and relevant for patients. However, a reliable cut-off point on a given comprehensive outcome instrument may not be easily defined or may require longer observation time than what can be realistically achieved in a clinical trial. Typically, the threshold needed to change clinical management or to arrive at a subsequent clinical stage or a functional endpoint serves this purpose. Number needed to treat indicates how many people need to be treated with a specific intervention for one person to experience a positive outcome. This measure is commonly used in assessing the effectiveness of treatments, and the number needed to treat to avoid progression to a more severe AD stage in the donanemab TRAILBLAZER-ALZ 2 trials, for example, was 10.[20] Number needed to harm represents the number of people who need to be exposed to a risk factor (e.g., a drug) for one person to experience an adverse outcome (e.g., a side effect). Responder analysis in clinical trials defines a responder based on a specific threshold of improvement. If a patient's outcome exceeds this threshold, they are considered a responder. Finally, time-to-event analysis (time saved) focuses on the time until a specific clinical event occurs (e.g., disease progression, relapse, or death). It quantifies the time saved by an intervention, for example, if a new treatment delays disease progression by 6 months compared to the standard treatment, that is the time saved. These analyses help researchers and clinicians understand the real-world impact of treatments and interventions. They guide decision making and improve patient care.

The monoclonal antibodies lecanemab and donanemab mark the first generation of effective DMTs for AD, representing significant research milestones.[21] However, the relatively modest effect sizes achieved during the restricted double-blind trial periods (mostly 18 months), potential side effects, implementation challenges in healthcare systems, and associated costs have sparked debates about their overall value. It is important to consider these aspects in context while recognizing the critical relevance of the new treatments in clinical care. AD is a highly complex disease with a long biological trajectory before symptom onset. It is unlikely that any other single molecular target treatment will have larger effects than those observed with amyloid-targeting antibodies in early AD stages with relatively minor symptoms. If the current trial effect sizes are deemed insufficient, future single molecular target treatments may also be considered inadequate. Significant improvements will likely be achieved incrementally over the years through continuous optimization and a combination of treatments. This process requires ongoing clinical use of these treatments and systematic longitudinal data collection from real-world

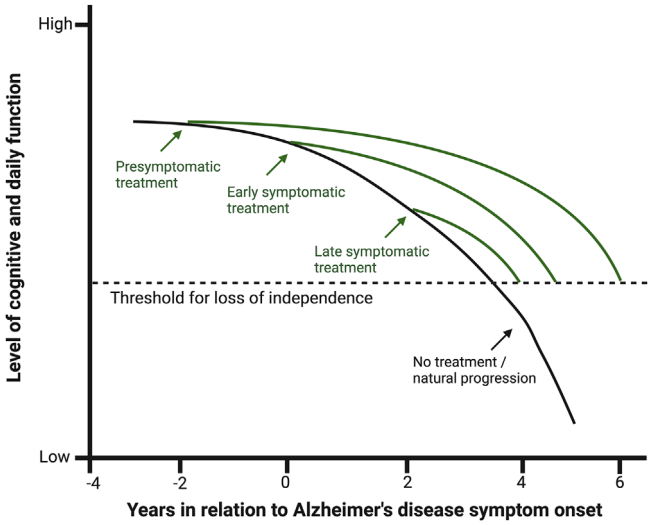

FIGURE 1 Hypothetical rates of cognitive and functional decline with (green solid lines) and without (black solid line) disease-modifying therapy. Earlier treatment results in a larger cumulative benefit over time compared to the natural disease progression. The threshold to losing independence and autonomy (black dotted line) is crossed later if treatment is started earlier (created with BioRender.com)

patients. Additionally, health-care systems must adapt to the new biological understanding of neurodegenerative diseases and evolve alongside the increasing complexity of diagnostics and treatments.

Evaluating the cost effectiveness of AD treatments is also crucial for determining their feasibility and value in real-world settings. Cost-effectiveness analyses compare the costs of treatments to their clinical benefits, such as improvements in quality of life and reductions in caregiver burden. For example, aducanumab was not estimated to be cost effective at the initial price of $56,000 even under ideal circumstances in which it completely halts AD progression; but in threshold analysis, it became cost effective at $22,820/year.[22] By incorporating these analyses, we can better understand the economic implications of new therapies and support informed decision making for health-care providers and policy makers. This approach ensures that treatments not only provide clinical benefits but also offer value for money, making them more accessible and sustainable in the long term.

4 | MEANINGFUL EFFECTS OF THE FIRST GENERATION OF ANTI-AMYLOID TREATMENTS

Anti-amyloid treatments aim to slow the biological and symptomatic progression of AD. Recent clinical trials have focused on patients with early symptomatic AD, including those with MCI and mild dementia. Biologically, early intervention is likely more effective than late-stage treatment because the spread and dynamics of the pathology are less advanced, and more brain tissue remains intact. Clinically, early treatment can help maintain a stage of less impairment, offering greater autonomy, higher independence, and lower direct and indirect care costs (Figure 1). The effectiveness of these new treatments in mod-

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erate and severe dementia is unclear and meaningful benefits are potentially less likely in more advanced diseases.

In the CLARITY-AD[23] and TRAILBLAZER-ALZ 2 studies, antibody treatments consistently and significantly slowed the rate of decline across all clinical outcomes compared to placebo. This was accompanied by a substantial reduction in cerebral amyloid load, reaching levels considered amyloid-negative in most participants. The primary endpoint scales showed a 27% reduction in decline for CLARITY-AD on the Clinical Dementia Rating Sum of Boxes (CDR-SB) in the overall population and a 35% reduction for TRAILBLAZER-ALZ 2 on the Integrated Alzheimer's Disease Rating Scale (iADRS) in the low tau population comparing the treatment to the placebo groups. The absolute differences in the CDR-SB were 0.45 points for lecanemab (primary endpoint) and 0.68 points for donanemab (key secondary endpoint) for the same comparisons.

The integration of real-world evidence into the evaluation of AD treatments is becoming increasingly important because it provides valuable insights into the effectiveness and safety of treatments in diverse, real-world populations, complementing the findings from randomized controlled trials. One notable example is the US Medicare's coverage with evidence development (CED) program, which has approved the use of current AD DMTs under specific conditions that require the collection of additional evidence.[24] This approach allows for the continuous assessment of treatment outcomes in a broader patient population, including those with comorbid conditions and varying levels of disease severity. By incorporating real-world evidence, researchers and clinicians can better understand the long-term impact of AD treatments, ensuring that the benefits observed in clinical trials translate to meaningful improvements in everyday clinical practice. This holistic approach enhances the relevance and applicability of trial results, ultimately leading to more informed treatment decisions and improved patient outcomes.

The clinical significance of observed effect sizes in AD treatments is a topic of ongoing debate. Tools such as the CDR-SB[25] and iADRS[26] measure critical aspects of AD, such as cognitive and functional impairment, which are central to the clinical presentation of the disease. Research has linked changes in the CDR-SB to clinically meaningful changes using external benchmarks. For example, a study using the US National Alzheimer's Coordinating Centers (NACC) database found that a change of 0.98 in MCI due to AD patients and 1.63 in mild dementia patients indicated a significant decline, based on clinician judgment.[27] Another study from the donepezil/vitamin E trial in MCI patients identified meaningful changes of 0.64 points (anchored to the MCI Clinical Global Impression of Change scale) and 1.08 points (anchored to the Global Deterioration scale).[28] These findings highlight variability in sensitivity to change between MCI and mild dementia, influenced by sample characteristics, data collection context, and chosen benchmarks. It is important to note that these benchmarks rely on clinician judgments, which may not be entirely reliable or valid, serving only as rough guidance. Moreover, clinically meaningful change is defined by health-care providers, not patients. In the TRAILBLAZER-ALZ 2 study, the placebo group showed a significant decline (1.82 points), while the donanemab group had a borderline clinically relevant deterioration (1.16 points).[20] Similarly, in the CLARITY-AD study, the placebo group experienced a substantial decline (1.66 points), whereas the lecanemab group showed a marginal reduction (1.21 points).[23] The higher proportion of MCI patients in CLARITY-AD compared to TRAILBLAZER-ALZ 2 might explain the smaller effect of lecanemab due to lower sensitivity of the CDR-SB in MCI.

Applying the principles of time-to-event analysis, the hazard ratios for progressing to a more severe clinical stage within 18 months were 0.69 for lecanemab for the overall population (31% risk reduction) and 0.61 for donanemab in the low tau group (39% risk reduction) and 0.50 for progression from moderate to severe dementia for donanemab.[20,23] This risk reduction is not only significant from a patient and caregiver but also from a societal perspective, given the increased care-related costs with advancing disease stages. For comparison, a meta-analysis of 92 FDA-approved anti-cancer drugs reported a hazard ratio for progression-free survival of 0.52.[29] Complementary approaches to assessing meaningfulness include subjective patient-oriented outcome measures. In the CLARITY-AD study, self-reported and care partner-reported quality of life and caregiver burden were assessed, showing significant superiority of lecanemab in both domains.[30] These points underscore the complexity of interpreting clinical meaningfulness in AD treatment studies and the importance of considering various factors and perspectives.

AD is a multifaceted condition influenced by various molecular mechanisms beyond the well-known amyloid and tau proteins. A comprehensive genome-wide association study pinpointed 75 loci significantly associated with AD risk. Analysis of these loci highlighted 33 gene clusters, emphasizing the substantial involvement of innate immunity and microglia-mediated endocytosis in AD.[31] AD is also exacerbated by environmental factors, lifestyle choices, and general aging processes.[32] As a result, research into potential treatments now encompasses areas such as inflammation, metabolic processes, oxidative stress mitigation, synaptic safeguarding, neurotransmitter equilibrium restoration, and protein homeostasis maintenance.[17] Given the complex origins of AD and its advanced state at initial symptom presentation, therapies targeting a single molecule during early symptomatic stages are unlikely to be markedly more effective compared to current amyloid-focused antibody treatments. It is anticipated that significant advancements will arise from combination therapies tailored to individual biomarkers and initiated at the earliest stages of the disease. This strategy implies that treatment improvements will be gradual over many years due to the lengthy nature of AD trials.

While biomarker-based assessments are valuable tools in AD research, they come with limitations that must be acknowledged. These include high costs, limited accessibility, and variability across different populations for established markers such as cerebrospinal fluid proteins and positron emission tomography measures of amyloid and tau. Such factors can impact the feasibility and generalizability of biomarker use in clinical practice. Addressing these limitations is crucial for advancing personalized medicine in AD. Efforts to reduce costs, improve accessibility, and ensure that biomarkers are validated across diverse populations will enhance their utility and ensure that they contribute meaningfully to patient care. Blood-based biomarkers will be

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more accessible than cerebrospinal fluid and imaging. In the context of communicating the meaningfulness of treatment effects to patients, effects on biomarker outcomes can convince patients that the medication affects the biology of the disease and that treatment effects can be expected to be sustainable.

One of the significant challenges in AD research is translating the slowing of cognitive or functional decline into outcomes that are meaningful to patients and their families. While regulatory bodies may accept "time-saved" analyses as meaningful, it is crucial to communicate these benefits in a way that resonates with patients and caregivers. In this context, early intervention with DMTs aims to preserve cognitive function before the onset of symptomatic disease. This proactive approach necessitates a shift in how we define and measure clinical meaningfulness. Traditional metrics may fall short in capturing the benefits of early intervention, as there may be no immediate symptomatic improvement to observe. Therefore, it is essential to develop and use patient-centric outcome measures that reflect the long-term benefits of sustained cognitive function and quality of life. Clear communication strategies must be used to help patients and caregivers understand the potential advantages of early DMT administration, despite the absence of immediate symptomatic relief. Even without symptoms, patients can report on their overall well-being, sense of purpose, and quality of life. Tools like the Meaning and Purpose Scales (MAPS) assess these aspects.[33] Tracking changes in biomarkers may also provide early indications of disease progression and treatment effects. This approach will ensure that the perceived value of treatment aligns with the clinical goals of slowing disease progression and maintaining cognitive health.

Conducting long-term trials for DMTs in AD involves significant challenges, such as retaining participants over extended periods and accurately measuring meaningful effects. Innovative trial designs, including adaptive trials and the use of digital health technologies for remote monitoring, can help mitigate these challenges. Additionally, addressing gaps in trial representativeness by including underrepresented populations and individuals with comorbidities is crucial for ensuring the generalizability of trial results. By implementing these strategies, researchers can enhance the robustness and relevance of long-term AD trials, ultimately leading to more effective and inclusive treatment approaches.

5 | INCLUSIVITY OF AD CLINICAL RESEARCH

Clinical trial populations are inherently biased toward healthier individuals, which can result in safety and effectiveness profiles of drug candidates that differ significantly from those observed in the general population.[34] This discrepancy can affect the perceived meaningful benefit of the drug and limit the generalizability of AD clinical trial results for the general population. To enhance the inclusivity and representativeness of AD clinical trials, it is essential to broaden eligibility criteria and focus on demographic diversity in recruitment through targeted outreach and education. By incorporating real-world data and long-term follow-up studies to the evidence from clinical trial results, we can ensure that the total body of evidence of trial results better reflects the demographics of those affected by AD.

Training clinical trial staff in cultural and language competency is another key strategy. This training enables staff to better understand and address the unique needs of diverse populations, fostering a more inclusive trial environment. Additionally, designing trials that accommodate participants' schedules and reduce the burden of participation, such as through telemedicine visits, can make it easier for a broader range of individuals to take part. Using targeted recruitment strategies to reach diverse populations, including partnerships with community organizations and local health-care providers, can significantly improve representation. Regularly monitoring and publicly reporting the diversity of trial participants can help ensure accountability and continuous improvement in inclusivity efforts. By implementing these strategies, clinical trials can become more inclusive, and their results more applicable to the general population. This inclusivity ultimately leads to better and more meaningful treatment outcomes for all patients, ensuring that the benefits of AD treatments are realized across diverse demographic groups.

Understanding and measuring value from the perspectives of patients and caregivers is crucial in evaluating meaningful benefits of AD treatments. Value in this context encompasses an assessment of trial design, the study population with a focus on inclusivity, and the relevance of the study endpoints. These should not only be clinical outcomes but also capture the overall impact on quality of life, daily functioning, and emotional well-being. Patient-reported outcomes play a vital role in capturing these dimensions, as they reflect the lived experiences and priorities of those directly affected by the disease. Additionally, incorporating caregiver-reported outcomes can provide a more comprehensive understanding of the treatment's impact on the caregiving experience, including the burden of care and the emotional and physical health of caregivers. Finally, the efficacy of study medication must be contextualized.[18] By integrating these perspectives with real-world evidence studies, researchers can ensure that the benefits of AD treatments are aligned with the needs and expectations of both patients and their caregivers and provide value. This patient-centric approach not only enhances the relevance of trial results but also supports the development of interventions that truly improve the lives of those affected by AD and may enhance the societal acceptance of the treatment.

6 | CONCLUSIONS AND OUTLOOK

The future of delivering meaningful benefits through AD drugs looks promising with several innovative approaches on the horizon. These approaches aim to enhance both the delivery and measurement of treatment benefits, ensuring they are truly impactful for patients. To measure the meaningful benefits of these treatments, researchers are developing multidimensional clinical outcome assessments. These assessments go beyond traditional cognitive and functional measures to include patient- and caregiver-reported outcomes, health and economic impacts, and neuropsychiatric symptoms. This comprehen-

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sive approach ensures that all aspects of a patient's well-being are adequately considered.[18]

The use of real-world data and longitudinal studies will be crucial in assessing the long-term effectiveness and safety of new treatments. By integrating data from diverse health-care settings and following patients over extended periods, research can gain a more accurate understanding of how treatments perform in everyday clinical practice. These innovative approaches, combined with ongoing advancements in AD research, hold great promise for delivering and measuring meaningful benefits for patients in the future. One example of a new global effort to use practice-based data is the International Registry for Alzheimer's Disease and Other Dementias (InRAD; https://www.inradnetwork.org), launched in March 2024 to effectively collect real-world data, based on a wide stakeholder consensus on a minimum and extended dataset to be collected, facilitating harmonization with other local registry efforts.[35] The Alzheimer's Network for Treatment and Diagnostics (ALZ-NET) registry of the US Alzheimer's Association (https://www.alz-net.org) is another example of a real-world AD data collection, aiming to harmonize registries in different countries (ALZ-NET International). By gathering extensive, standardized data globally, an international registry will offer crucial insights into disease progression, treatment effectiveness, and patient outcomes. It will encourage collaboration among various stakeholders, promote knowledge sharing and innovation, and facilitate patient recruitment for clinical trials. Additionally, it will provide real-world evidence of treatment effects and safety, addressing gaps left by clinical trials that often exclude certain patient populations and have limited follow-up periods.

An international registry will also help identify patients most likely to respond to specific treatments, allowing for a more personalized approach to care. Long-term tracking of patient outcomes will provide insights into optimal treatment strategies. Moreover, standardized biomarker assessments will facilitate the early detection of AD, enabling earlier intervention and more effective treatment. The comprehensive practice-based evidence from an international real-world data registry will help identify patterns and characteristics of patients who are more likely to benefit from new DMTs. This includes demographic measures, disease progression markers, genetic factors, and more. Without such a registry, the necessary data are unlikely to be available from routine medical records, and local or national registries will not achieve the complete picture that global real-world data collection can provide. By tracking the long-term outcomes of treated patients, the registry will offer valuable insights into optimal care strategies, such as the best time to start (and stop) treatment, dosage adjustments, and managing side effects. The registry will also serve as a platform for post-marketing surveillance, monitoring the safety and effectiveness of DMTs in a real-world setting. This will lead to an earlier identification of potential issues and ensure that the benefits of a drug continue to outweigh any risks.

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CONFLICT OF INTEREST STATEMENT

R.P. has received honoraria for advisory boards and speaker engagements from Roche, EISAI, Eli Lilly, Biogen, Janssen-Cilag, Astra Zeneca, Schwabe, Grifols, Novo Nordisk, and Tabuk; and was principal investigator on the aducanumab phase-III trials. L.F. has received grants, consultancy fees, or lecture honoraria from Biogen, Eisai, Grifols, Hummingbird, InfectoPharm, Janssen-Cilag, Merck Sharpe & Dohme, Neurimmune, Neuromodulation, Noselab, Novo Nordisk, Roche, TauRX, and Schwabe; has served on Data and Safety Monitoring boards with Otsuka, Pharmatrophix, Forschungszentrum Jülich, Charité Berlin, Neuroscios, and Vivoryon; was principal investigator on the lecanemab phase-III trial; and is a co-author on the publication of the lecanemab phase-III study data.[23] Author disclosures are available in the supporting information.

CONSENT STATEMENT

No consent for human subjects was necessary.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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