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PERSPECTIVE

Decision making in clinical trials: Interim analyses, innovative design, and biomarkers

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Abstract

The efficient and accurate execution of clinical trials testing novel treatments for Alzheimer's disease (AD) is a critical component of the field's collective efforts to develop effective disease-modifying treatments for AD. The lengthy and heterogeneous nature of clinical progression in AD contributes to the challenges inherent in demonstrating a clinically meaningful benefit of any potential new AD therapy. The failure of many large and expensive clinical trials to date has prompted a focus on optimizing all aspects of decision making, to not only expedite the development of new treatments, but also maximize the value of the information that each clinical trial yields, so that all future clinical trials (including those that are negative) will contribute toward advancing the field. To address this important topic the Alzheimer's Association Research Roundtable convened December 1–2, 2020. The goals focused around identifying new directions and actionable steps to enhance clinical trial decision making in planned future studies.

KEYWORDS
Alzheimer's disease, amyloid, clinical meaningfulness, clinical trial, cognition, cognitive impairment, dementia, biomarkers, futility analysis, interim analysis, mild cognitive impairment, tau

1 | INTRODUCTION AND OVERVIEW

The past few decades have brought enormous advances in our understanding of Alzheimer's disease (AD) pathophysiology, which in turn have led to valuable new directions in both research and clinical care. A shift toward a biological research framework,[1] in which AD is defined by proteinopathies[2] and neuropathological changes rather than by a manifest clinical syndrome, has not only facilitated standardized reporting in observational and interventional trials, but has also provided a common language that has helped to harmonize and increase the efficiency of efforts by a wide range of international research entities. The need for similar advances that will bring us closer to effective treatments is increasingly urgent. Currently, ≈55 million people worldwide are living with dementia (the majority of whom have AD), a number that is projected to rise to 139 million in 2050 as the global population ages, and in 2019 the global cost to society was estimated to be more than (US)$1.3 trillion.[3]

Despite enormous scientific progress in other areas of the field, innovation in the design and execution of AD clinical trials is more sparse. Current trial designs, most of which involve lengthy periods of blinded evaluation of a large number of participants, have often not produced successful outcomes, have proven to be extraordinarily

expensive, have limited the number of drugs and targets that can be tested, and are ultimately not sustainable. To reexamine important aspects of clinical trial decision making with the aim of guiding the field toward much-needed answers, the Alzheimer's Association Research Roundtable (AARR) convened December 1–2, 2020. This meeting provided a forum for experts from academia, industry, patient advocacy, and regulatory agencies to explore decision making from multiple and converging angles, with a focus on potential new uses of biomarkers, interim analyses, and innovative clinical trial designs, as well as on the ethical and regulatory considerations that must guide next steps.

Over the last decade, biomarkers that are predictive of neuropathology have come to play a major role in determining eligibility for AD clinical trials. However, biomarkers also have the potential to play increasingly important roles in driving the development of disease-modifying treatments for AD. Before biomarkers can be used to further increase the efficiency and power of clinical trials, and perhaps ultimately signal the early success or futility of various treatments (i.e., guiding go/no-go decisions), further work must be done to ascertain detailed relationships between biomarkers and clinical outcomes, including how these relationships change over the course of AD.[4] Current research aimed at refining our knowledge of the temporal order in which neuropathologic and neurodegenerative events occur in AD, and the degree to which individual biomarkers accurately represent those events, will likely generate information that can be used to improve the design and analysis of future prevention trials in AD. Toward that end, researchers are investigating how biomarkers might be used to delineate individual trajectories of disease progression, pinpoint optimal targets and windows of treatment for preventive interventions, and provide data that can predict clinical outcomes. Although the successful and even transformative use of biomarkers in other therapeutic areas—particularly in oncology—is a cause for optimism, the uncertain relationship of AD biomarkers to clinical trial outcomes continues to pose unique challenges.

To justify continued effort and avoid exposing clinical trial participants to unnecessary risks and inconvenience, many randomized clinical trials require and benefit from periodic monitoring and decisions based on futility and other interim analyses. When thoughtfully planned and skillfully executed, such analyses can help investigators confidently arrive at critical early decisions. Some recent uses of futility analyses, however, both inside and outside of the field of AD,[5] suggest that a reexamination and refinement of these statistical tools is necessary to improve the quality of decision making in clinical trials. The retrospective use of clinical trial data from studies terminated for futility, which occurred in the case of aducanumab, the recently approved anti-amyloid monoclonal antibody,[6–8] has raised questions about substantial evidence of efficacy and/or a clinically meaningful benefit, and pointed to the need for the judicious, cautious, and consequential use of this type of interim analysis.[9] At a time when there is an urgent need for disease-modifying treatments, it is essential that the AD scientific community aligns strategies for using interim analyses to enhance the flexibility and responsiveness of clinical trials without sacrificing scientific integrity.

RESEARCH IN CONTEXT

1. **Systematic review**: The Alzheimer's Association convened a workgroup of experts to identify new directions and actionable steps to enhance clinical trial decision making in planned future studies.
2. **Interpretation**: Interim analyses are used as a decision point in clinical trials to ascertain whether the study should continue or stop due to futility or efficacy, but the timing of such analyses should be carefully considered, as should the methodology of such planned analyses.
3. **Future directions**: Review and consideration of emerging data sets and biomarkers can help inform the field of the risks and timing of planning for interim analysis.

2 | BIOMARKERS TO IMPROVE THE STUDY OF THE CORRECT PATIENTS

The establishment of a biological framework for AD research has moved the field forward considerably, in large part by defining AD as a set of neuropathological changes that can be measured in vivo by biomarkers before clinical signs and symptoms develop. These biomarkers enable a much earlier and more certain diagnosis of AD compared to conventional diagnosis, which was based only on clinical signs and symptoms. It has been estimated that prior to the establishment of this framework, ≈ 10% to 30% of individuals entering clinical trials who received a clinical diagnosis of AD dementia lacked evidence of AD-specific neuropathologic changes at autopsy or based on findings from amyloid positron emission tomography (PET) or cerebrospinal fluid (CSF) amyloid beta $(A\beta)_{42}$ studies.[1,10] Indeed, many early failed clinical trials may have been hampered in part by the inclusion of participants who did not have the targeted pathology or had insufficient levels of the targeted pathology.[11]

AD research has benefitted from the validation of biomarkers that can be used to confirm the presence of AD pathology, and also from the use of the A/T/N (amyloid/tau/neurodegeneration) classification scheme[1] to stage the neuropathological progression of clinical trial participants and, in turn, further refine clinical trial populations. Efforts to understand which key biological events are represented by changes in biomarkers, as well as details regarding the relationships among various biomarkers during the course of disease, are expected to increase the value of using biomarkers to enhance decisions regarding clinical trial eligibility, and also improve our ability to predict disease progression, ascertain target engagement, and predict clinical outcomes.

2.1 | Advances in clinical trial eligibility, tau PET imaging, and blood-based biomarkers

The process of eligibility screening for most clinical trials targeting Aβ to date has involved the use of two validated biomarker tests for

amyloidosis. Potential clinical trial participants who meet appropriate clinical criteria now typically undergo amyloid PET or CSF $A\beta_{42}$ (or $A\beta_{42}/A\beta_{40}$) testing to determine whether they are on the AD biological continuum.[12] Although routine screening for the presence of amyloid represents significant progress, major drawbacks to current amyloid biomarkers include significant cost, lack of availability, lack of precision, and invasiveness.[13] Many biomarkers currently under development or undergoing refinement aim to address issues of cost, availability/scalability, and convenience/tolerability as well as the need to more accurately stage disease, ascertain distinct AD phenotypes and corresponding trajectories of disease, and predict disease progression and clinical outcomes.

The addition of tau PET as a screening tool for eligibility in clinical trials is a welcome development that likely will help to increase the power and efficiency of newer clinical trials of anti-tau and anti-amyloid agents.[14,15] Tau PET imaging may prove to be a valuable tool in anti-amyloid trials, where it may be used to address concerns that anti-amyloid treatments might have limited efficacy in advanced AD, as evidenced by the presence of significant tau pathology. In such trials, tau PET may increase the power of anti-amyloid clinical trials when used as a tool to exclude trial participants with extensive tau deposition. It has been postulated that low levels of tau-PET signal may predict that a participant is less likely to show decline in a clinical trial and therefore decrease power.[16]

Because many individuals with AD pathology also have substantial vascular and other pathology,[17] it will likely also be necessary to quantify these pathologies. The simplest approach, limiting enrollment to individuals with AD pathology only, may prove too restrictive and will not reflect the real-world context of multiple disease comorbidities. Efforts to guide the type or amount of each component of a multidimensional intervention have been established in some risk reduction and prevention trials, such as the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability study.[18]

Significant progress in the development of sensitive assays to detect AD pathology (phosphorylated tau and $A\beta$) in plasma is pointing to promising new tools on the horizon for detecting early AD and differentiating between AD and other forms of dementia.[19–21] These rapid, non-invasive, and relatively inexpensive forms of assessment will represent a huge advancement in clinical trial recruitment and also in the clinical diagnosis of AD. Additional research will be needed to further validate these biomarkers, to optimize these assays, and to test findings in unselected and diverse populations against PET, CSF, and neuropathology.

2.2 | Predicting disease progression

Individuals with clinically defined mild cognitive impairment (MCI) have a significantly increased risk of developing dementia, often caused by AD,[22] and it has been estimated that approximately half of all people who receive a diagnosis of MCI will go on to develop dementia within approximately 3 years.[23,24] However, as many as half of individuals with MCI may remain stable and, in some cases, may, at least temporarily, experience a return to relatively normal cognition. Accordingly, people who meet the criteria for MCI may experience a lengthy period of uncertainty, during which their prognosis may be unclear.

Slow and variable rates of progression during the early stages of AD also present significant challenges in clinical trials by confounding or limiting the detectable magnitude of treatment effects. Biomarkers capable of predicting progression would be a particularly valuable tool for AD clinical trials.[25] To date, amyloid PET and CSF amyloid have not proven to be sufficient predictors of progression, at least at an individual level. Biomarker evidence of amyloid alone cannot provide adequate information about whether an individual will go on to experience cognitive decline in the short term (i.e., over the duration of a typical double-blind clinical trial), or about the rate at which individuals with AD will experience disease progression.[26]

One promising approach to individualized prognosis involves the use of a panel of biomarkers to predict how progressed individuals are along the disease continuum and their future cognitive decline. A recent study[27] used CSF and volumetric magnetic resonance imaging (MRI) biomarkers to develop and validate a multimodal biomarker fingerprint that produces individualized progression curves in a pre-dementia population (980 cognitively unimpaired or MCI individuals from the French MEMENTO study and Alzheimer's Disease Neuroimaging Initiative [ADNI]). The utility of combinations of plasma biomarkers of $A\beta$, tau, and neurodegeneration was studied in two other recent studies. These studies used cognitively unimpaired individuals and MCI patients from the Swedish BioFINDER study and ADNI, demonstrating that combinations of plasma biomarkers both predicted future cognitive decline and subsequent dementia in cognitively unimpaired individuals and conversion to dementia in patients with MCI.[28] Such combinations of biomarkers are promising for improving the efficiency with which one can conduct clinical trials in preclinical and prodromal AD. The ability to enroll individuals predicted to have large future decline can substantially reduce sample size requirements, and the utility of plasma biomarkers in cognitively unimpaired individuals may enable much more efficient recruitment in clinical trials aimed at preclinical AD by means of minimally invasive large-scale screening. What could still be challenging is determining whether a given therapeutic strategy has similar or different effects among individuals with higher versus lower rates of progression, and the risk that faster progressors may be less likely to benefit from a given intervention.

2.3 | Demonstrating disease modification and predicting clinical outcome

The most sought-after biomarkers or groups of biomarkers in AD research are those that could qualify as theragnostic surrogates, or biomarkers that are reliably and highly predictive of a clinical outcome in response to an intervention (as opposed to diagnostic or prognostic biomarkers). To date researchers have yet to obtain definitive evidence that a change in any AD biomarker or group of markers in response to

a therapeutic intervention can predict clinical benefit, largely because of an absence (until recently) of AD trials with clear clinical benefit. In contrast, other therapeutic areas have successfully identified biomarkers that clearly correlate with clinical outcomes; in the field of oncology, for example, a reduction in tumor burden within a given time frame has been correlated with longer survival. Finding equivalent AD biomarkers will be a more complex undertaking, as there are multiple processes leading to the disease. The cascade of biomarkers in AD is believed to proceed from amyloid to tau to neuronal loss and then to cognitive impairment.[29] Adding to the complexity, there may be a time lag from a biomarker change to a clinical change. Changes in markers of neuronal injury and neurodegeneration, presumably being more proximate to patients' symptoms, are expected to correlate more strongly with clinical outcomes, making them promising surrogate markers of disease modification.

Current US Food and Drug Administration guidance requires that a biomarker must be validated across different mechanisms of action and must associate with improvement (or reduced decline) in cognition to be used as a surrogate outcome measure.[30] A possible solution, with regulatory approval, may be to draw from evidence supporting the use of a particular biomarker in other therapeutic areas. For example, neurofilament light chain (NfL), a neuron-specific cytoskeletal protein that has shown promise as an early and independent marker for future cognitive changes in an AD clinical trial setting,[31] has already been linked to benefits in multiple sclerosis (MS).[32,33] Studies used to validate such biomarkers must be designed to have a large enough effect size to demonstrate a clear association between a change in the biomarkers and clinical benefit.

2.3.1 | Novel cognitive assessments and disease modelling

Cognitive changes represent an important, highly relevant outcome to measure in AD trials.[34] However, many cognitive assessments traditionally used in AD clinical trials suffer from floor/ceiling effects and linguistic limitations, require some subjective interpretation, and are susceptible to practice effects. Furthermore, because individuals commonly experience daily fluctuations in cognition related to conditions such as stress, lack of sleep, test anxiety, fatigue, and other health conditions, it can be challenging or impossible to capture information that reliably reflects cognitive decline related to AD.

To address these issues, recent strategies involve the use of digital technology for the administration of cognitive assessments through an individual's own device (e.g., smartphone) or another internet interface, permitting highly nuanced measures of cognition, function, and behavior.[35,36] Such methodology is being applied in clinical trials of early-stage AD and one example is undergoing validation using the Knight Alzheimer's Disease Research Center cohort. All assessments have been compared to standard in-clinic cognitive tests and with AD biomarkers including amyloid PET, CSF tau, tau PET, and structural MRI. The smartphone and web-based measures have demonstrated associations with each of these AD biomarkers.[37] Reliance on short-term, high-frequency testing provides hope of achieving greater reliability and validity compared to standard in-clinic cognitive assessments. This suggests that remote high-frequency assessments may hold promise as clinical outcome metrics.

Repeated evaluation of cognition in individuals over time can also be used to develop disease progression models that may eventually predict not only disease stage but also future cognitive decline in individuals who do not yet have measurable cognitive deficits.[38] The model of Raket[38] acknowledges that the cognitive capability of an individual with AD at any given time reflects not only the disease state, but also a range of variables including the patient's pre-morbid cognitive capability and demographic variables such as age, sex, education, medical comorbidities, family history, and genetics. Disease progression models relying only on cognitive assessments can predict a patient's disease stage with high reliability only after a systematic pattern of cognitive decline has been observed. However, combining longitudinal cognitive scores with individual patient biomarker profiles enables identification of biomarker fingerprints that are predictive of disease stage and future decline.[39] Results suggest that biomarker profiles at a single time point can be used to predict the disease stage and future decline of an individual even in the preclinical phases of disease, when no clinically detectable cognitive impairment is present. With further validation, these results may be used to define biomarker profiles for use as inclusion criteria in clinical trials. Such biomarker-based synchronization of patients' disease stage might enable the testing of a drug in a more clinically homogeneous population, allow for better management of missing data during clinical trials (as this is based on modeling an individual's progression), and would, in turn, greatly increase the power of clinical trials in AD where it is otherwise common to see extreme levels of variability in patient trajectories.[40,41]

2.3.2 | Insights from the field of oncology

Significant strides toward targeted therapies and personalized medicine in the field of oncology during the past two decades are an important source of inspiration for the AD field. After many disappointments, the therapeutic armamentarium in oncology is rapidly expanding and the number of new agents under development is steadily rising. These successes can be traced to revolutionary shifts in thinking and collaboration with regulatory agencies that led in turn to the creation of new frameworks for faster and more successful testing of therapeutics.

A more recent paradigmatic shift in oncology has occurred in the field's clinical classification of disease. Cancers are now less frequently categorized based on their site of origin, and instead tend to be categorized based on mutations and genetic alterations that lead to the development of a cancer.[42] This move toward a biological classification of disease in turn inspired novel clinical trial designs that moved the field in the direction of targeted therapies and personalized medicine. At least two new clinical trial designs that were first developed in oncology, biomarker-guided basket trials and umbrella trials,[43] have been adapted for use in the AD field.[44–46]

3 | EFFICIENT DESIGN AND ANALYSES

Several current trends in AD clinical trials suggest the need for changes in clinical trial design to increase efficiency, in part by enabling investigators to arrive at critical answers earlier. During the past decade, AD clinical trials have grown larger in size and longer in duration, which require the use of enormous resources, to detect sometimes small effects on tests such as Alzheimer's Disease Assessment Scale Cognitive subscale (ADAS-Cog)[47] or Clinical Dementia Rating Scale (CDR),[48] typical primary endpoints (or components thereof). There is a growing consensus that exorbitantly expensive studies such as these, which involve a high degree of financial risk and must be precisely designed and executed, are unsustainable.

3.1 | Enhancing the value of interim/futility analyses

In an effort to limit risk or increase efficiency, many Phase IIb/III AD trials include interim analyses to arrive at earlier answers, as well as stopping rules that use formal statistical methods for evaluating interim data and determining whether a study may or should be stopped early.[49] If interim data provide compelling evidence of treatment efficacy or if a significant difference between experimental and control groups is unlikely to be obtained, pre-planned rules may guide early stopping of a trial.[50] To ensure that accurate decisions are made, it is essential that appropriate planning guides the proper interpretation of early data and ensures that assumptions about future data that would be observed after the interim analysis are carefully evaluated and robust.

Because investigators and stakeholders prefer to see studies completed, a general bias against interim analyses exists. Stopping a trial early for futility based on interim data could result in the loss of potentially valuable information. As long as there is uncertainty about the treatment duration required to demonstrate a benefit, it will remain challenging to discern futility from insufficient treatment duration until the trial is nearly complete, at least for trials with a common close design that maintain double-blind study drug treatment for everyone until the end of the study. Moreover, in recent years, simulations using data from cohort studies for prevention trials of cognitively normal individuals suggest some studies need a longer treatment phase to achieve high statistical power.[38,51] However, study designs that permit statistical inferences only after a trial is complete can be impractical, associated with significant financial risks as well as potential risks to participants.

3.2 | Potential/future use of biomarkers in futility analyses

The use of biomarkers to enhance decision making in futility analyses has not been extensively explored or well defined. However, valuable data that may lead to progress in this area are being obtained in Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU) and ADNI.[52,53] The allure of using biomarkers as potential decision-making tools in futility analyses stems from drugs whose targets (or key downstream effectors) may be tracked by biomarker assessments. To be attractive for futility decision making, several characteristics must be true of a biomarker: it should be related to clinical efficacy and should demonstrate longitudinal change with lower variance or at an earlier time point than clinical endpoints (otherwise, clinical endpoints would remain preferred). The DIAN-TU clinical trials have formal futility analyses designed around a biomarker that would lead to high predictability between a biomarker and clinical outcome, although the degree to which amyloid or tau accumulation must be reduced, and the length of time that they may need to be suppressed for a clinically relevant outcome, are not certain.

3.3 | Innovative trial designs

In recent years, the AD field has been moving toward clinical trial designs with greater efficiency. Adaptive trial designs allow investigators to learn from an ongoing trial and modify the trial while it is in progress. Most adaptive trials incorporate prospectively planned modifications to one or more design elements based on accumulating trial data,[54–56] thereby increasing the efficiency via smaller sample sizes or shorter study duration. They may also facilitate the study of rare diseases or personalized treatments of patient subgroups with specific genotypes or phenotypes. Clinical trials that target multiple mechanisms and pathways may add significantly to the complexity of interim analyses, especially if a trial's goals include measures of clinical status and safety. A notable downside to some of these advanced trial designs is that the statistical analysis and interpretation of data can become much more complex. Often statistical properties of the trial outcomes must be simulated, and simulation results are only as good as the assumptions of these scenarios. While one can try to simulate a wide range of scenarios, there are infinitely many scenarios in which data do not match the assumptions of the simulations. This doesn't mean the design is not adapting to those scenarios dynamically. The key assumptions when designing Bayesian trials are the same as for fixed trial designs, including anticipated effect size and variability in the trial.

4 | REGULATORY AND ETHICAL CONSIDERATIONS

Both research and clinical practice in AD are evolving as the field shifts from a clinical definition to a biological approach to AD. Accordingly, pivotal Phase III trials are not only geared toward arriving at effective treatments, but by design also help with validating disease definitions, further validating "A/T/N" criteria[1] and improving our understanding of the natural history of relevant subgroups. Assessments of disease and of treatment effects in individuals with AD involve a great degree of complexity and therefore pose a number of challenges.

As the field moves forward there is a critical need to address a number of challenges regarding communication with patients. A particular concern is that the language of "benefit" in the field of AD, for clinicians and patients alike, is somewhat opaque. AD affects dimensional measures such as cognition, function, and behavior—unlike in other therapeutic areas, in which hallmarks of a disease, such as an infarct or the fracture of hip, are easier to measure and to understand. Likewise, biomarkers in the field of AD can have ambiguous value, unlike biomarkers such as tumor size, bone mineral density, or low-density lipoprotein levels, which can be more tightly linked to a language of clinical benefit. In addition, the current therapeutic goal in AD disease modification is the slowing down of disease progression, for which the clinical benefit must be expressed compared to a historic or current control group and in most cases cannot be observed at an individual patient level. Consideration must be given to the most appropriate strategies for communicating uncertainties in the field so that patients are equipped to make decisions that are as well informed as possible. Likewise, efforts must be made to communicate to patients considerations (including uncertainties) that surround decisions to stop a clinical trial or analyze a trial for potential futility.[57]

In a similar vein, patients ought to be as well informed as possible about all tests that are used in clinical trial decision making, including those used in clinical trial randomization or in decisions regarding the dosing of drug. Efforts along these lines already have been made in recent AD trials, such as the A4 study, in which individuals with elevated amyloid are informed of their status and properly counseled. Under the auspices of the Alzheimer's Association, an important group known as the Participant FIRST (Follow-Up Improvement in Research Studies and Trials) work group, has published recommendations to improve communication with research participants in case trials end early and identifying supports for those affected by early trial closure.[58]

5 | CONCLUSION

The topics presented at the Fall 2020 Alzheimer's Association Research Roundtable continue to be a critical part of clinical trial design and decision making in clinical trials, and discussions during this Topic Meeting helped guide the field toward solutions. We continue to identify shortcomings with the current designs of AD clinical trials, despite notable evolution over the past decade and more. As recruitment methods and treatment designs result in increased costs and timelines, the sustainability of the current designs becomes more challenging and cost prohibitive.

Interim analyses are used as a decision point in clinical trials to ascertain whether the study should continue or stop due to futility or efficacy. The benefits of these analyses appeal to a variety of stakeholders, including sponsors and regulatory agencies, especially when considering the time and resources invested in global Phase III clinical trials. But the timing of such analyses should be carefully considered, as should the methodology of such planned analyses. Review and consideration of emerging data sets can help inform the field of the risks and timing of planning for interim analysis. Biomarkers continue to change the ways in which we conduct clinical trials. There is optimism in biomarkers' ability to identify specific windows of eligibility for clinical trials participation, track disease progression, and inform interim analysis. Plasma biomarkers offer hope for a tool that can perform reliable, accurate, and cost-effective measurements throughout a study. More validation is needed, though, before such biomarkers can be effectively implemented for decision making in clinical trials.

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CONFLICT OF INTEREST STATEMENT

C.J.W. and M.C.C. are full-time employees of the Alzheimer's Association. G.A.K. is a full-time employee and shareholder at F. Hoffmann-La Roche, Ltd. K.W.B. has received grants or contracts from WCG Clinical Endpoint Solutions, and payment or honoraria from Biogen & Roche/Genentech. D.S.M. is a full-time employee and shareholder of Signant Health, past Chair of the Alzheimer's Association Research Roundtable, and Co-Chair of the ISCTM BPSD Work Group. E.R.S. has received consulting fees from Biogen, Cogstate, Cortexyme, Partner Therapeutics, Pinteon Therapeutics, Vaccinex, Acumen Pharmaceuticals, Gates Ventures, and Hoffman LaRoche; participated in a DSMB for Hoffman LaRoche; held leadership roles with the Alzheimer's Association and BrightFocus Foundation; and is a shareholder for Acumen Pharmaceuticals. F.N. is a full-time employee and shareholder of Eli Lilly and Company. M.G. and W.R. do not have any disclosures. L.L.R. is a full-time employee of Eli Lilly, and was a full-time employee of Novo Nordisk during the development of this manuscript. Author disclosures are available in the supporting information.

CONSENT STATEMENT

As there was no experimentation with human subjects as part of this manuscript, no consent was obtained (or 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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