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PERSPECTIVE

Operationalizing selection criteria for clinical trials in Alzheimer's disease: Biomarker and clinical considerations: Proceedings from the Alzheimer's Association Research Roundtable (AARR) Fall 2021 meeting

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Abstract

The design of clinical trials in Alzheimer's disease (AD) must consider the development of new plasma, cerebrospinal fluid (CSF), and imaging biomarkers. They must also define clinically meaningful outcomes for patients and set endpoints that measure these outcomes accurately. With the accelerated United States Food and Drug Administration (FDA) approval of the first anti-amyloid, disease-modifying treatment for AD, a monoclonal antibody called aducanumab, the landscape of clinical trial design is evolving. Enrolment in clinical trials may be impacted by the availability of this and other treatments, and trial design must take into consideration that patients may desire a disease-modifying treatment rather than potentially being randomized to the placebo arm. The Alzheimer's Association Research Roundtable (AARR) Fall 2021 meeting discussed the consideration of well-defined AD staging criteria in protocol design and how they influence more standardized inclusion/exclusion criteria for trials, as well as what constitutes meaningful differentiation between the stages. Discussion explored the current state of knowledge regarding biomarkers and how they can inform AD staging criteria, as many trials are now designed based on specific biomarker features, further underscoring the importance of coordinating AD staging criteria and biomarkers. The relationship between cognition and biomarkers has been studied and this must continue as trials move forward. Researchers, patients, clinicians, regulatory scientists, and payers discussed the state of the field as well as the future of symptomatic Alzheimer's disease clinical trials.

KEYWORDS
Alzheimer disease, amyloid, biomarkers, clinical trial, cognition, cognitive impairment, dementia, mild cognitive impairment, MCI, tau

Highlights

- The Alzheimer's Association Research Roundtable (AARR) convened leaders from academia and industry as well as patients, care partners, clinicians, regulators, and payers to discuss the topic of operationalizing selection criteria for clinical trials and the role of biomarkers.
- Well-defined Alzheimer's disease (AD) staging criteria are an important consideration in study protocol design.
- Staging criteria and biomarkers must be coordinated to yield high-quality clinical trial results that have meaning for patients with AD by selecting a population most likely to benefit from a specific treatment.

1 | INTRODUCTION

The Alzheimer's Association Research Roundtable (AARR) convened leaders from academia and industry as well as patients, care partners, clinicians, regulators, and payers to discuss the topic of operationalizing selection criteria for clinical trials and the role of biomarkers. Biomarkers in Alzheimer's disease (AD) include brain imaging (such as positron emission tomography, or PET), plasma measurements, and cerebrospinal fluid (CSF) proteins.

Here we report on the proceedings of the AARR meeting where stakeholders considered the role of clinical measures of progression, how a single biomarker may prove to be a reliable surrogate for multiple biomarkers, how patients' staging criteria may define their biomarker profile, the benefits of creating a global standard for AD staging criteria, and results from recent AD clinical trials which may inform selection criteria for new trials.

In 2021, the field of AD experienced the first (accelerated) United States Food and Drug Administration (FDA) approval of a disease-modifying treatment, aducanumab,[1] a monoclonal antibody that targets the buildup of amyloid in the brain. In 2023, lecanemab was approved for AD[2] with other, similar in class drugs potentially on the horizon.[3] That has changed the landscape of research and clinical trials in the field, including a renewed focus on early detection and diagnosis of AD, as well as development of additional therapeutics. There is also the possibility that the approval will enhance the potential for trials of combination therapies. Approval of new treatments also brings some challenges, such as impacting ongoing trials where patients may withdraw from a clinical trial to take newly approved treatments. New trials must consider eligibility criteria and acceptability of treatment initiation with the newly approved treatments either prior to or during the clinical trial. AD staging criteria still lacks standardized, empirical definitions. Well-defined AD staging criteria are an important consideration in study protocol design. These will lead to more standardized inclusion/exclusion criteria and the ability to differentiate between stages in a meaningful and objective way. Many ongoing and future trials are being designed on the basis of biomarker features in combination with some clinical criteria. The two—staging criteria and biomarkers—must be coordinated to yield high-quality clinical trial results that have meaning for patients with AD by selecting a population most likely to benefit from a specific treatment.

1.1 | Harmonizing the 2018 NIA-AA Framework and 2018 FDA Guidance in clinical trial designs and operationalizing toward recruitment and measurement

The 2018 National Institute on Aging/Alzheimer's Association (NIA-AA) Research Framework[4] and 2018 FDA Guidance[5] may differ in how they conceptualize AD and how they view symptomatology and biomarkers, but they complement each other as well. Utilizing the frameworks to guide clinical trial design necessitates a deep understanding of how they complement each other and where they overlap, thus showing how both documents can work together harmoniously when used to design, recruit and measure outcomes in clinical trial.

In the NIA-AA Research Framework, AD refers to pathologic changes in the brain, and the symptoms of AD are considered a result of the disease process and therefore do not define the disease (i.e., amnestic dementia and AD are not synonymous). AD itself is defined by the measurement of biomarkers in vivo. In creating the framework, the authors intended to harmonize the pathology gold standard with the in vivo definition, anchoring the in vivo diagnosis via biomarkers to the well-accepted, traditional gold standard of pathological diagnosis.

The core principles of the 2018 FDA Guidance include that AD is a single disease that exists on a continuum. The Guidance was research-focused, with its core purpose being the selection of patients with early AD for enrollment in clinical trials, as well as endpoint selection. Similar to the NIA-AA Framework, the definition of AD is primarily a biological one, with symptoms being the eventual result of the disease process.

With the emergence of plasma biomarkers, the field must revise the implicit concept of equivalence among fluid and imaging biomarkers within the amyloid/tau/neurodegeneration [AT(N)] groupings. Accumulating evidence indicates that particularly for the T category, we must be cautious when interpreting biomarkers, as biofluid and imaging markers of tau pathology may not be interchangeable.[6]

Measures used to define AD must be specific to AD, but staging biomarkers need not be specific for AD. Cognitive/clinical and biomarker staging are two separate staging domains that ought to be considered separately in evaluating patients. The interface of biomarker and clinical staging is a rich area of ongoing exploration.

Regarding the biomarker definition of AD, the language used in the FDA Guidance is conceptual, while the NIA-AA Framework uses operational language. As biomarkers evolve, there is no change required to the FDA Guidance—it remains receptive and useful as the field moves forward. It is the role of the scientific community to revise and define the operational definition as needed, and that was the intention with each of the guidance documents. These two efforts are complementary and will harmonize together as the field moves forward.

In particular, the use of plasma biomarkers is advancing rapidly, and the field is on the verge of using a variety of plasma biomarkers for not only screening but patient selection and enrollment for clinical trials.[7] The challenge is to integrate the plasma biomarkers with the AT(N) scheme in a way that recognizes the differences between imaging and fluid biomarkers.

1.2 | Clinical assessments, subject selection, and staging: where are we headed?

When looking at using clinical assessments to help stage patients and select subjects for clinical trials, it's important to consider clinical meaningfulness.[8] If clinical outcome measures can be used to demonstrate changes that are clinically meaningful, that could represent an acceptable single primary endpoint for a trial. Researchers might consider whether they can build meaningfulness into the outcome itself. This can be complicated with neuropsychological tests and other assessments that show a fine gradation of effect, as they may detect minor changes that are of questionable meaningfulness. It is important to consider whether the treatment has affected a core domain or is doing something meaningful for a patient.

When those same measures are utilized longitudinally, the character of how that data are used takes on a different dynamic. Tracking a particular measure over time helps get at the core character of the disease, leading to a deep and reliable understanding of how the disease might progress. "Minimally clinically important differences," or MCIDs, tend to reflect "real-time" assessment; that is, what happens when you take the drug in real time. If we make meaningfulness inherent in the measure itself that's being used, we may be able to move away from using MCIDs.

The opposite problem occurs when disease-modifying treatments slow the disease down in ways that may be meaningful and relevant to a patient, but might not show much change on the scale used to measure progression. If a treatment leads to a 6-month delay in progression and a patient is able to continue to drive, shop, and cook, that is clinically meaningful for them. A point on a scale means nothing to a patient if not actualized in real life. Furthermore, one cutoff for everyone in clinical measures does not take into account the heterogeneity of presentation of patients, particularly early in the course of the disease. Some patients in the early stages report issues other than memory as their biggest concern, including executive dysfunction, visuospatial dysfunction, and other early symptoms.[9]

Including underrepresented populations in clinical trials is an important part of moving the field forward. Broader inclusion criteria can help capture this population, but we are still identifying the domains that we need to consider (e.g., education level). Researchers do not yet understand what are the first cognitive domains that are affected in these populations.[10] As researchers, our norms must be sound. We want to be able to include subjects with higher education who are not yet performing at a low enough level to meet criteria, but still have declined significantly from their baseline.

As researchers continue to utilize clinical assessments, keeping clinical meaningfulness at the forefront of our minds is key. Understanding that our tests and scales must have relevance to the patients and their families who want to take recently-approved drugs and see their effects in real time, with real impact on their day-to-day life, is critical. Developing and refining assessment tools that get at clinical meaningfulness in a real way and that reflect the multiple domains of functioning that are affected, not just memory, will be important as the field moves forward.

1.3 | The role of biomarkers in disease staging

In the past several years, multiple biomarkers have been developed that help determine a patient's current stage of AD.[11,12] At the same time, there is substantial heterogeneity in how biomarkers correlate with clinical progression of AD. The biomarkers will tell you that the patients will progress, but not necessarily when they will progress. Still, biomarkers play an important role in staging, whether definitive or enriching.

Rather than being able to narrow the field down to a single biomarker, the biomarkers can be used together to provide complementary information. A two-step approach could be used, for example, where tau PET helps inform us on clinical progression,[13] but when combined with plasma biomarkers measuring axonal degeneration (neurofilament light chain [NFL]) or reactive astrocytes (glial fibrillary acidic protein [GFAP]), it will present a more complete picture.

Eventually, plasma biomarkers may become the primary means by which we diagnose and stage AD. But the field still has further to go before we reach that point. Plasma biomarkers have been tested in controlled laboratory conditions. Now they must be tested in real-world conditions with real-world variability induced by, for example, medical comorbidities and batch-to-batch variation. They must be scaled and standardized so that results can be reproduced from lab to lab with precision. Given the speed with which plasma biomarkers are advancing, it's critical to ensure consistency across labs and assay platforms. Data are being collected on plasma biomarkers now, and as more and more data are aggregated, this will help the field standardize these biomarkers.

To reduce heterogeneity in studies, biomarkers must be considered in the context of state, trait, and stage. Amyloid biomarkers are useful for "trait" (whether a patient has AD or not).[14] For staging of disease, tau biomarkers are going to be very important—in particular, tau PET. Tau PET indicates how far the tangles have progressed in the neocortex and is likely to turn out to be an important measure of prognosis or future cognitive trajectory.[15] The degree of tau PET uptake in the brain at baseline may also be an important predictor of the patient's response to different targets, for example amyloid-lowering targets, as removal of amyloid may be less impactful once tau is at a certain point of accumulation[16] Tau PET thus might may become an important stratifier in biologically staging the disease and helping to make the results clearer to interpret.

In the future, it seems likely that the field will have different (sets of) biomarkers for each stage of AD. Amyloid PET may not be as effective at staging people who are symptomatic versus preclinical. Tau aggregation PET-positivity is not commonly detected by tau PET in the preclinical population, but is useful for staging in symptomatic patients. CSF and plasma p-tau biomarkers show a higher sensitivity in early stages of AD and therefore perform quite differently from tau PET, rising above the threshold of detection earlier in the disease continuum. There is much complexity here that will take time and effort to tease out. Plasma biomarkers may be best for initial screening in preclinical AD, as they are likely more cost-effective than PET. But to determine later stages may require additional biomarkers and imaging.

Scaling biomarkers from clinical trials to clinical practice is a difficult challenge, one that needs to accommodate the new availability of disease-modifying drugs. Once the field accepts that this is the new environment, we can learn and adapt.

There may be multiple ways to get to a definition of early Alzheimer's disease. It could rely on a single plasma biomarker or a single PET scan to confirm pathology. But for some patients, simply obtaining their amyloid status may be sufficient to characterize them from a clinical point of view. For other more complex clinical scenarios, an additional test such as tau PET may be needed after the amyloid biomarker. Continued dialogue in the research community is needed to determine the best path forward to interpret the data for best use criteria.

It is important to bear in mind that, even if we reduce plaque load to zero on PET, we may not have completely stopped the progression of the disease. Researchers must consider the complex pathology that is AD. We may need to take a multi-pronged approach and consider what else to measure besides the amyloid plaque load present on PET. There may also be other targets yet to be identified, such as vascular pathology and neuroinflammation. There are multiple amyloid species that may be part of the disease process that are not eliminated by a single anti-amyloid therapy. PET might not pick up some species, and anti-amyloid antibodies bind to some specific species but not others. It is possible that the amyloid species that remain could be contributing to the disease process.

Furthermore, prevention trials might yield a stronger disease-modifying effect. Potentially, the earlier we treat, the more responsive the disease may be. The ideal time to intervene may be earlier than symptoms appear. More research is needed here.

1.4 | Amyloid and tau biomarkers and the prediction of clinical outcomes

The natural history of biomarker changes over the course of AD, particularly tau versus amyloid, indicates that amyloid plays a role in increasing the rate of production of excess tau.[17] We postulate that lowering amyloid levels changes the process that stimulates production of new excess tau. Thus, by lowering amyloid levels we slow the rate of production of tau. But what makes the amount of tau actually decrease? This is the riddle, where the rate constant of elimination of excess tau is presumed to happen. There is some process, possibly microglial activities, that will slowly remove tau over time if we reduce the production of amyloid. What remains unanswered is why amyloid itself modulates the production rate of tau. Research is still trying to understand the underlying mechanism.

By developing quantitative models based on the amyloid/tau/neurodegeneration framework,[4] one can simulate the time-course of amyloid and downstream biomarkers corresponding to active and placebo groups in clinical trials of anti-amyloid therapy. These models have been developing since the 1990s and have evolved significantly over time. As biomarkers evolve, quantitative models will also evolve.[18] Plasma biomarkers are an important contribution to modeling, allowing access to longitudinal data sets that will be helpful in evaluating biomarker utility. As we collect more data sets, the models will become better informed and hopefully more accurate.

Fluid biomarkers help researchers scale trials to large data sets and yield large quantities of data, but the high accuracy and regional information provided by imaging is what has yielded key insights into the disease process itself. The cost and speed of trials using plasma biomarkers is a significant benefit. But we must understand: how do plasma biomarkers predict cognitive changes? We need a mechanistic model that will explain how fluid biomarkers change and how they relate to the pathology detected by imaging biomarkers. The two do not measure the same thing—they may be correlated, but one may change more rapidly over time, while the other is a slower, accumulating effect. Mathematically, they are not interchangeable. If we could create a mechanistic picture where these pieces represent the disease, its underlying physiology and pathophysiology, that might be the future of modeling.

1.5 | Considerations in participant selection, design, and implementation of clinical trials

With the approval of the first amyloid-targeting antibodies, the design of clinical trials is changing. New strategies are needed, which may include: combination therapy, add-on therapies, head-to-head comparisons, and looking at patient subpopulations and/or disease-stage specific treatments. Considerations when designing combination

clinical trials include factorial design, dosing sequence of combination therapies, and how to do dose ranging studies when evaluating multiple doses.

Combination therapy can look different depending on the therapeutics being used. For other diseases, combination therapy may mean one pill containing fixed-dose combinations of two or more substances.[19] In AD, we are more likely to see multiple monoclonal antibodies or other treatments that will require separate administration of two substances with separate prescriptions. A design might include one tau-directed drug and one anti-amyloid drug. Most anti-amyloid monoclonal antibodies that remove amyloid plaques show remarkably similar results in terms of magnitude. The impact on disease progression of a combination therapy could be additive, synergistic, or interfering.

As the field moves toward precision medicine, trials will hopefully target specific patient subpopulations or disease stages. Ideally, we will know which patients to target by phase 2 trials (instead of waiting until phase 3 and then having to restart treatment in the subpopulations). More work is needed to understand which patients and stages might preferably respond to treatments. Any of the other strategies like add-on or head-to-head can also be applied to subpopulations.

As we look at where we want trials to go in the future, some key issues are clear. Establishing Standard of Care is important before implementing add-on trials, particularly for comparative efficacy trials. It is also critical to determine what results are required from monotherapy before combination therapy is considered. One could imagine factorial designs[20] implemented with more than one investigational drug, or approved drugs not yet deemed standard of care.[21] We will need to decide on the balance between biomarker evidence and scientific evidence of clinical efficacy. We will need to consider whether tau monoclonal antibodies and other therapies that have failed phase 2 might be relaunched as add-on therapy.

The outcome of combination trials must demonstrate the contribution of each molecule in the combination. A range of biomarkers may be best suited to do this. In addition, the patient selection biomarkers are important not only to confirm diagnosis and select the appropriate stage for the targets of the therapeutics being tested, but also to help understand if there is a synergistic or interference effect between the two therapeutics.

In the event that an FDA-approved therapy becomes Standard of Care, there will still remain a role for placebo-controlled trials, particularly because the inclusion criteria are often increasingly narrow.[22] Other disease fields such as multiple sclerosis show how this can be done.[23] Patients who enroll in placebo-controlled trials in this scenario might include patients who fall outside the criteria employed in the original trials, patients who decline the approved therapy, those who fail to respond to the approved therapy, and even those patients who fully understand the risks yet wish to delay approved therapy to contribute to scientific understanding.

When considering novel design trials like adaptive trials, there is some evidence from other fields that with appropriate education of the scientific value of these designs, patients can appreciate and understand the benefits and are willing to participate in these types of trials.[24] Patients may be more willing to enroll in a study with a placebo arm if they know that they are likely to be assigned to an effective treatment later on in the study (e.g., open-label extension phase).

It is difficult for the field of AD research to develop efficient platform designs for clinical trials. Compared to a field like oncology, AD faces challenges with duration of recruitment, duration of screening, and duration of follow-up. Existing cohorts with early onset sporadic AD, who typically have fewer comorbidities, may be particularly well-suited for these types of trials (though this is a fairly small population). They show more rapid change in both biomarkers and clinical outcomes, which might enable shorter trials with fewer participants.[25] Thus they may be a population that can participate in more efficient platform designs.

The field must overcome the challenges of the past, including failed clinical trials, and reunite to regain the trust of patients. Currently, in the absence of a Standard of Care, placebo-controlled trials remain ethical.[26] Informed consent of participants is a critical component of ethical study conduct, regardless of design.[27] Active-controlled (non-inferiority or superiority design) trials, in particular, factorial designs, may be key to the field's ultimate therapeutic goals, and may become the norm in the future. They will help us understand the effects of various combinations of drugs and whether they are additive, synergistic, or competitive.

1.6 | Relationship of biomarkers and cognitive measures: Considerations of clinical meaningfulness

With the hope that, in the near future, we will have several therapeutics to choose from and a greater number of clinical trials, clinical care will need to evolve as well. Education of primary care providers is key, helping them understand the importance of detecting cognitive decline and not dismissing it as "normal aging" or other features. Primary care physicians (PCPs), specialists in family medicine or general internal medicine who provide definitive care to patients at point of first contact,[28] will need to screen for mild cognitive impairment (MCI) and be able to diagnose it. Potentially, digital tools will be available that can help assess cognition, and biomarkers can help with the diagnosis and confirm the presence of amyloid. The field is just starting this journey in terms of improving diagnosis and care for PCPs, helping them learn to communicate accurately on prognosis and available options for therapeutics, clinical trials, and other approaches to slow progression and/or treat.[29]

A critical question that must be addressed is whether biomarkers can predict whether the efficacy of the compound will lead to a favorable clinical outcome. Also, how do the biomarkers relate to signaling paths that lead to clinically meaningful outcomes? Thus far, correlation has been shown between changes in amyloid and changes in cognition,[30] but these need to be verified in confirmatory trials. Over the next 2 years, larger clinical trials with rich biomarker data are being conducted that will hopefully answer this. At the same time, correlated data have major limitations, and we need to continue to search for casual mechanistic explanations.

With an insidious disease like AD, clinicians often tell patients they may not see symptomatic improvement, but rather a slowing of progression that may not be apparent to them. Biomarkers in practice may give us a way to say the treatment is "doing something" even if the patient is not aware of the difference. The more individualized data we can give patients, the more we can motivate them to stay in clinical care on a particular course of treatment. Biomarkers validated through a clinical trial will help inform patients and their families of a therapeutic benefit. This could instruct patient education but also treatment choices (e.g., when to stop or change a drug). One of the big benefits for patients who participate in a trial is learning more about themselves. These are important opportunities to improve the way we conduct trials, select subjects, and impact practice.

One path to evolve research in AD is by looking for synergies between our research structure and our clinical care. The more we do this, the more we will be able to facilitate structured observation in the environment. At that point, routine clinical care becomes research-grade. We can collect long-term data that will provide important insights to patients, providers, and payers.

2 | CONCLUSION

While amyloid (A), tau (T), and other neurodegenerative biomarkers (N) are key pieces of the puzzle, there are clearly intermediate players between A and T, T and (N), and (N) and cognition. We are hoping to understand the great variability between amyloid and tau changes, and what accounts for individual variability in the tau versus amyloid trajectory. Modeling, theorizing, and testing will help us know where to look and how to fill in those gaps in our understanding.

While there have been many advances in the understanding of the underlying biological processes with AD and the newer research diagnostic classifications are more focused on biological biomarkers, we cannot ignore the core symptomatology of worsening cognition and memory that first brings the patients and their families to seek medical care. The current approved medications not only require the diagnosis of AD but also the disease stage that the patient is experiencing. Preclinical AD, MCI due to AD, as well as mild, moderate, and severe AD are stages that have been defined based on cognition. The relationship between cognition and biological biomarkers has been and continues to be studied under the Alzheimer's Disease Neuroimaging Initiative (ADNI) that was started by M. Weiner in 2004.[31] While ADNI and other trials continue collecting both biological biomarkers as well as objective cognitive measurements from longitudinal AD cohorts, there will still be a need to evaluate both biomarkers and cognition as part of the clinical trial inclusions for new drug development and clinical application of approved AD treatments.

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CONSENT STATEMENT

Consent (i.e., all human subjects provided informed consent) was not applicable.

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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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