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Guidance for Sponsors
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Quantitative Neuroimaging of Alzheimer's Disease

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An estimated 7.2 million Americans aged 65 and older are living with Alzheimer's dementia in 2025, at a cost to the nation of about $384 billion.[1] For most of the past century the diagnosis was clinical and could only be confirmed at autopsy. That has changed. Amyloid PET, tau PET, volumetric MRI and, since 2025, FDA-cleared blood tests now define the disease biologically while a patient is alive, and the first disease-modifying antibodies are approved. Quantitative neuroimaging has moved from a research tool to the backbone of how Alzheimer's trials enroll, treat and monitor patients. This issue explains the imaging biomarkers sponsors must plan for.

From a Clinical to a Biological Diagnosis

Alzheimer's disease is defined by two pathologic hallmarks: extracellular plaques of beta-amyloid and intraneuronal neurofibrillary tangles of hyperphosphorylated tau. In 2024 the Alzheimer's Association Workgroup published revised criteria that formally define the disease by its biology rather than by symptoms. Under these criteria, a positive Core 1 biomarker, such as amyloid PET or an accurate plasma p-tau217 assay, is sufficient to diagnose Alzheimer's disease, and Core 2 biomarkers, chiefly tau PET, are used to stage its progression.[2]

This shift matters for trial design. Historically, as many as a quarter of patients enrolled in Alzheimer's trials on clinical grounds alone turned out to have no amyloid pathology. Biomarker confirmation at screening is now expected by regulators, and every approved anti-amyloid therapy requires it in its label.[3]

Amyloid PET and the Centiloid Scale

Three fluorine-18 amyloid tracers, florbetapir, flutemetamol and florbetaben, are FDA approved for estimating neuritic plaque density. Because each tracer has different reference regions and uptake characteristics, the Centiloid project established a common 0 to 100 scale that converts any tracer's standardized uptake value ratio into a shared unit, with 0 representing young amyloid-negative controls and 100 representing typical Alzheimer's dementia.[4] Centiloids make amyloid reduction comparable across tracers, sites and trials.

Amyloid clearance is now itself a regulatory endpoint. Lecanemab received traditional approval in July 2023 after the Phase 3 Clarity AD trial showed a 27 percent slowing of clinical decline alongside substantial amyloid reduction on PET.[5] Donanemab followed in July 2024; its TRAILBLAZER-ALZ 2 trial used tau PET to stratify participants and allowed treatment to stop once amyloid PET fell below a defined threshold.[6] In both programs, central quantitative PET reading was essential to the result.

Tau PET and Staging

Flortaucipir, approved in May 2020, is the first PET tracer for aggregated tau neurofibrillary tangles.[7] Unlike amyloid, which plateaus early, tau burden tracks closely with neurodegeneration and cognitive decline, and its regional spread follows a predictable pattern from the medial temporal lobe to the neocortex. Trials increasingly use tau PET to select participants at a particular stage, as donanemab's pivotal study did, and as an exploratory endpoint for disease modification.

Structural MRI: Volumetry and Safety

Volumetric MRI quantifies atrophy of the hippocampus, entorhinal cortex and whole brain, and remains a well-established secondary endpoint. Standardized 3D T1-weighted acquisitions, consistent scanner assignment and

automated segmentation with longitudinal registration are required to detect annualized changes of one to two percent.

MRI has also become a safety biomarker. Amyloid-related imaging abnormalities (ARIA) occur with all anti-amyloid antibodies, appearing as vasogenic edema or sulcal effusion (ARIA-E) or as microhemorrhage and superficial siderosis (ARIA-H). The donanemab label requires a baseline MRI within one year of starting therapy and MRIs before the second, third, fourth and seventh infusions, with dosing suspended or stopped depending on ARIA severity, and it carries a boxed warning.[3] Lecanemab's label contains similar requirements, and in July 2026 the FDA approved an at-home subcutaneous starting dose, which extends ARIA monitoring into community settings.[8] For sponsors this means a protocol-defined MRI schedule with T2*-weighted or susceptibility-weighted sequences, FLAIR, and radiologists trained in standardized ARIA grading.

Blood Biomarkers Join the Toolkit

In May 2025 the FDA cleared the Lumipulse plasma pTau217/beta-amyloid 1-42 ratio test, the first blood test to aid diagnosis of Alzheimer's disease; in the pivotal study, 91.7 percent of positive results were confirmed by amyloid PET or CSF.[9] A second plasma p-tau217 assay was cleared in 2026.[10] Blood tests are now an efficient prescreening step that reduces the number of amyloid PET scans needed to enroll a trial, but PET remains the reference for confirming eligibility and for quantifying treatment response.

Guidance for Sponsors

Imaging an Alzheimer's trial

- **Confirm pathology at screening.** Use amyloid PET or a validated plasma assay with PET confirmation, consistent with the 2024 biological criteria.[2,9]
- **Report amyloid in Centiloids.** Use the common scale so results are comparable across tracers and sites.[4]
- **Consider tau PET for staging.** Stratify or select participants by tau burden where the mechanism warrants it.[6,7]
- **Build the ARIA schedule into the protocol.** Follow label-based MRI timing and use standardized ARIA grading.[3]
- **Standardize volumetric MRI.** Fix the 3D T1 protocol, keep participants on the same scanner and use longitudinal segmentation.
- **Read centrally.** Use blinded independent central review with neuroradiologists experienced in amyloid, tau and ARIA interpretation.[11]

Summary

Quantitative neuroimaging now defines who has Alzheimer's disease, who enters a trial, whether a drug clears its target and whether treatment is safe to continue. With two approved antibodies, a biological diagnostic framework and blood tests feeding into PET confirmation, sponsors have more tools than ever, and more reasons to plan their imaging carefully from the first protocol draft.

About the Author

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