

Critical Path for Alzheimer's Disease: Reducing Uncertainty Before the First Patient Enrolls

→ PROBLEM

In 2026, an estimated 7.4 million Americans age 65 and older are living with Alzheimer's dementia, most surviving four to eight years after diagnosis.¹ After two decades without a disease-modifying therapy, FDA granted traditional approval to lecanemab in 2023 and donanemab in 2024 for early symptomatic disease.² That progress raises the stakes on trial design. Of an estimated \$42.5 billion in private clinical-stage spending from 1995 to mid-2021, 57% went to late-stage trials, where a design error is most expensive and least recoverable.³

Some failures are failures of design, not biology. Alzheimer's advances for years before symptoms become obvious, and at different rates in different people. Developers must decide whom to enroll, how many participants they need, what to measure and how long to follow them. Flawed assumptions may not surface until the trial ends, years later. The evidence to make better choices existed but was scattered across completed studies in incompatible formats. The field could learn within programs but not across them.

→ SOLUTION

In 2008, Critical Path Institute (C-Path) launched the Critical Path for Alzheimer's Disease consortium to solve a problem no sponsor could solve alone. No company held enough data to model the disease or could convene competitors to pool it. The work required a neutral organization with no product in development and the patience to standardize data for years before it could answer a single question. We brought industry, researchers and regulators together in a precompetitive setting, built an integrated patient-level database in 2010, and helped establish disease-specific data standards in 2011 so studies could be analyzed together.⁴

From that shared data, we built disease-progression models and clinical trial simulation tools that let sponsors test patient selection, study size, clinical measures, follow-up time and variability before finalizing a protocol. The database holds de-identified records from 12,811 participants across 36 Alzheimer's disease and mild cognitive impairment trials, available to consortium members and approved outside researchers.^{5,6}

What we built: an integrated drug-development resource

CORE CAPABILITY	WHAT WE BUILT	VALUE FOR DRUG DEVELOPMENT
Data collaboration	Neutral, precompetitive consortium convened in 2008	Joint work on barriers that cross company boundaries
Standardized evidence	Integrated patient-level database (2010) and disease-specific data standards (2011); records from 12,811 participants across 36 trials	Cross-study analysis and controlled research access
Quantitative modeling	Disease-progression models and trial simulation tools for pre-dementia and mild-to-moderate disease	Testing protocol assumptions before enrollment
Regulatory science	Biomarker and model proposals advanced through review in the U.S. and EU	Agency-recognized uses and direction for further development
Ongoing methodology	Harmonization of tau measurements across brain scans	Extends the resource toward endpoints for future trials; work ongoing

→ OUR APPROACH: TESTING THE TRIAL BEFORE THE TRIAL

Our simulation tools use the pooled data to reproduce realistic disease progression, variability and dropout, so sponsors can test a proposed design against virtual cohorts and see whether it could detect a treatment effect of a given size. Designs that would yield uninterpretable results can be caught while they are still inexpensive to change.^{6,7} The question shifts from what a trial found to what it was ever capable of finding.

DESIGN DECISION	WHAT SIMULATION TESTS	WHY IT MATTERS
Patient selection	Whether the enrolled population declines quickly enough to show separation	A treatment signal can be lost in a population that does not progress
Study size	Participants needed to detect a plausible effect	An underpowered trial returns a negative result that says little about the drug
Follow-up time	Time required for a treatment effect to emerge	A readout taken too early may miss a real effect
Clinical measures	Sensitivity of the measure to change at that disease stage	The instrument chosen may not capture benefit that is present
Dropout	Effect of attrition on power and interpretability	Attrition reduces statistical power and can bias the remaining cohort
Variability	Expected range of progression across participants	Between-patient variation shapes how large an effect must be to detect

→ IMPACT

Beyond data sharing, we engaged U.S. and European regulators on how imaging measures and simulation models could be used in drug development. Qualifications and fit-for-purpose determinations endorse specific, defined uses; letters of support flag promising approaches that warrant further evidence.^{4,7}

YEAR	REGULATORY MILESTONE	WHAT THE MILESTONE ENABLED
2011	EU qualification of low hippocampal volume	An imaging measure to help select participants for trials before dementia
2013	U.S. fit-for-purpose finding and European qualification	Specified uses of a disease-progression and trial-simulation model in mild-to-moderate Alzheimer's disease
2015	U.S. letters of support	Further evaluation of spinal-fluid markers and hippocampal volume for patient selection
2017-2018	U.S. and EU letters of support	Further work on model-based patient selection and simulation in mild cognitive impairment

Together, these milestones delivered a qualified imaging measure, a trial-simulation model recognized for defined uses by regulators in both regions, and agency support for research in earlier disease stages. They give the field reusable methods where any one sponsor's evidence is necessarily limited.^{4,7}

The shared resource continues to support new research. In 2025, Novo Nordisk used our Alzheimer's database to study body-weight patterns and trial dropout in early disease.⁸ Data contributed years earlier helped answer a question no one had posed when it was collected, which is the defining trait of an evidence base that outlives a single trial.

Advantages of evidence designed for reuse

C-Path connects capabilities that are usually separate: neutral collaboration, standardized patient-level data, quantitative modeling and regulatory engagement. Together, they help sponsors test design choices earlier and give completed studies a role in future research. We are now applying the same approach to align tau measurements across brain scans and evaluate their potential as future trial endpoints.⁶

Key takeaways

- 1** We convene the field. A neutral, precompetitive setting unites industry, researchers and regulators around barriers none can address alone.
- 2** We make data reusable. Common standards turn separate trials, including unsuccessful ones, into a resource that answers questions no one asked at the time.
- 3** We connect evidence to regulatory science. Qualification, fit-for-purpose findings and agency feedback define uses for tools and chart a path for further study.
- 4** We build beyond one milestone. Sponsor research now runs on the database, and our tau imaging work extends it toward future trial endpoints.