Design

CLINICAL TRIALS

Clinical Trials
1–10

DOI: 10.1177/17407745211034497
journals.sagepub.com/home/ctj
SAGE

On the design of early-phase Alzheimer's disease clinical trials with cerebrospinal fluid tau outcomes

Michelle M Nuño[1,2], Joshua D Grill[3,4,5*], Daniel L Gillen[3,6*] for the Alzheimer's Disease Neuroimaging Initiative

Abstract

Background/Aims: The focus of Alzheimer's disease studies has shifted to earlier disease stages, including mild cognitive impairment. Biomarker inclusion criteria are often incorporated into mild cognitive impairment clinical trials to identify individuals with "prodromal Alzheimer's disease" to ensure appropriate drug targets and enrich for participants likely to develop Alzheimer's disease dementia. The use of these eligibility criteria may affect study power.

Methods: We investigated outcome variability and study power in the setting of proof-of-concept prodromal Alzheimer's disease trials that incorporate cerebrospinal fluid levels of total tau (t-tau) and phosphorylated (p-tau) as primary outcomes and how differing biomarker inclusion criteria affect power. We used data from the Alzheimer's Disease Neuroimaging Initiative to model trial scenarios and to estimate the variance and within-subject correlation of total and phosphorylated tau. These estimates were then used to investigate the differences in study power for trials considering these two surrogate outcomes.

Results: Patient characteristics were similar for all eligibility criteria. The lowest outcome variance and highest within-subject correlation were obtained when phosphorylated tau was used as an eligibility criterion, compared to amyloid beta or total tau, regardless of whether total tau or phosphorylated tau were used as primary outcomes. Power increased when eligibility criteria were broadened to allow for enrollment of subjects with either low amyloid beta or high phosphorylated tau.

Conclusion: Specific biomarker inclusion criteria may impact statistical power in trials using total tau or phosphorylated tau as the primary outcome. In concert with other important considerations such as treatment target and population of clinical interest, these results may have implications to the integrity and efficiency of prodromal Alzheimer's disease trial designs.

Keywords

Alzheimer's disease, inclusion criteria, biomarkers, trial design

Introduction

Alzheimer's disease (AD) is the most common cause of dementia, cognitive impairment that impacts daily life.[1] It is estimated that 50 million people had AD in 2018.[2] No disease-modifying therapies are available for AD; thus, the United States and other nations have developed plans to address AD, most of which mandate the need for research to develop treatments to slow or stop the disease progression.[3]

AD is characterized by deposition in the brain of two hallmark neuropathologies: neuritic plaques and neurofibrillary tangles.[4] Plaques are formed by the

[1]Children's Oncology Group, Monrovia, CA, USA
[2]Department of Preventive Medicine, University of Southern California, Los Angeles, CA, USA
[3]Institute for Memory Impairments and Neurological Disorders, University of California, Irvine, Irvine, CA, USA
[4]Department of Neurobiology and Behavior, University of California, Irvine, Irvine, CA, USA
[5]Department of Psychiatry and Human Behavior, University of California, Irvine, Irvine, CA, USA
[6]Department of Statistics, University of California, Irvine, Irvine, CA, USA

Corresponding author:
Michelle M Nuño, Department of Preventive Medicine, University of Southern California, 800 Royal Oaks Dr. Suite 210, Monrovia, CA 91016, USA.
Email: mnuno@childrensoncologygroup.org

extracellular accumulation of the amyloid beta protein; neurofibrillary tangles result from hyperphosphorylation of the microtubule-associated protein tau. These proteins can be measured in cerebrospinal fluid or visualized in the brain through positron emission tomography scans.[5] Studies using these biomarkers demonstrate that AD pathology develops over time, beginning prior to the diagnosis of dementia. Amyloid accumulation may be detectable before tau and may peak earlier in disease.[6] In contrast, neuropathological[7,8] and biomarker[9,10] studies independently support that tangle deposition more closely correlates with disease progression. Thus, tau phosphorylation and spreading may represent ideal therapeutic targets in AD,[11,12] while tau-related outcome measures may be generally useful for trials of potential disease-modifying therapies.

Efforts to intervene earlier in the disease have led to the conduct of trials enrolling participants with mild cognitive impairment, cognitive impairment that does not affect activities of daily living. The pattern of cerebrospinal fluid changes associated with AD, specifically lower levels of amyloid beta and higher levels of total and phosphorylated tau are associated with progression to AD dementia in patients with mild cognitive impairment.[13,14] Based on these findings, diagnostic criteria for mild cognitive impairment due to AD,[15] or prodromal AD,[16] were proposed for patients with mild cognitive impairment and a biomarker profile consistent with AD.[17,18] Although this general diagnostic construct has been applied in several clinical trials,[19–22] the specific biomarker criteria utilized have varied from study to study. Implementing different inclusion criteria can affect participant eligibility and, in turn, affect study enrollment and power.[23]

Investigators would benefit from additional information to use in designing prodromal AD trials. In particular, added data examining the distribution of longitudinal changes in tau biomarker outcomes are needed, as well as information on how specific biomarker inclusion criteria may impact longitudinal observations. These decisions have clear implications to early-stage studies, such as phase 2 proof-of-concept trials where surrogate biomarkers are commonly used as primary outcomes and go/no-go decision points for larger confirmatory phase 3 studies. These trial designs require estimates of within-subject changes over time and between-subject variability for biomarker outcomes to ensure adequate power and sample size calculations. For trials of anti-tau therapies[24] with cerebrospinal fluid measures of total and phosphorylated tau as the primary outcomes, few such data are available.

In this study, we sought to use available longitudinal data to instruct designs and quantify plausible power in phase 2 proof-of-concept trials in prodromal AD for which the primary outcome is total or phosphorylated tau measured in cerebrospinal fluid. Our goal was to provide data for study planning, including the variance and within-subject correlations. We also set out to investigate how various inclusion criteria impact study power. The design and statistical methods were selected to reflect those commonly used in prodromal AD trials.[19,21,25,26]

Methods

Study population

Data used in preparation of this manuscript were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu) on 9 March 2020 from http://adni.loni.usc.edu/data-samples/access-data/. For up-to-date information, see www.adni-info.org. Our study included participants from ADNI-1, ADNI-2, and ADNI-GO with at least two cerebrospinal fluid measurements, one of which had to be obtained at baseline. Furthermore, participants must have been eligible based on at least one of the cerebrospinal fluid eligibility criteria (as described in the following section) and must have had a diagnosis of amnestic mild cognitive impairment at baseline. ADNI implemented Petersen diagnostic criteria for mild cognitive impairment,[27] including requiring subjective memory complaints but little or no impairment in daily function.[28] Participants must have also satisfied ADNI inclusion criteria, which can be found at www.adni-info.org. Study participants provided written informed consent.

Biomarker criteria

Our study considered a hypothetical, two-arm, prodromal AD study using total tau or phosphorylated tau as the primary outcome. In this hypothetical study, only participants with mild cognitive impairment who meet biomarker criteria would be eligible. In particular, we focused on eligibility criteria based on cerebrospinal fluid measures of amyloid beta, total tau, and phosphorylated tau. We incorporated multiple biomarker inclusion criteria, including low amyloid beta, high phosphorylated tau, high total tau, and adequately high ratios of phosphorylated tau to amyloid beta. Cerebrospinal fluid measurements were obtained using the AlzBio3 assay and thresholds from Shaw et al. (2009) were used to determine eligibility based on each criterion.[29] These thresholds required that participants had levels below 192 pg/mL, above 93 pg/mL, and above 23 pg/mL on cerebrospinal fluid amyloid beta, total tau, and phosphorylated tau, respectively. To be eligible based on the ratio of phosphorylated tau to amyloid beta, participants had to have a ratio above 0.10. We focused on five sets of eligibility criteria for prodromal AD trials: adequately low amyloid beta, adequately high total tau, adequately high phosphorylated tau, low amyloid beta or high phosphorylated

tau, and low amyloid beta or high phosphorylated tau to amyloid beta ratio.

Analyses

We considered a hypothetical 2-year, fixed sample, two-arm, placebo-controlled, randomized phase II study with 50 subjects (n = 25 subjects per arm) for each set of eligibility criteria. In this study, participants are assigned to a treatment group via 1:1 randomization. The outcome is measured at baseline (before randomization) and at 2 years (after randomization). In this hypothetical scenario, we assumed investigators would be testing whether there is a treatment effect on a biomarker outcome using a common analysis of covariance (ANCOVA) model[30] of the form

$$E[Y_{1i}] = \beta_0 + \beta_1 Y_{0i} + \Delta Tx_i \quad (1)$$

where Y_{0i} and Y_{1i} denote the outcome measures at baseline and 2 years, respectively, and Tx_i is an indicator for whether subject i received the treatment. That is, Tx_i is one if subject i was randomized to the treatment arm, and 0 if the subject was randomized to the placebo or control arm. Hence, Δ in equation (1) represents the treatment effect and can be interpreted as the average difference in the 2-year cerebrospinal fluid measurement (for total tau and phosphorylated tau) between treatment and control groups for subpopulations with similar baseline measurements.

Under the ANCOVA model given in equation (1), power of a two-sided level α test of the null hypothesis $H_0 : \Delta = 0$ for rejecting the hypothesized alternative Δ_1 can be calculated as

$$Power(\Delta_1) = \Phi\left(\frac{-\Delta_1}{\sqrt{4(1-\rho^2)\sigma^2/n}} - z_{1-\alpha/2}\right) + 1 - \Phi\left(\frac{-\Delta_1}{\sqrt{4(1-\rho^2)\sigma^2/n}} + z_{1-\alpha/2}\right) \quad (2)$$

In equation (2), the number of subjects in each arm is denoted by n, ρ denotes the 2-year within-subject correlation between response measures, and σ^2 denotes the variance of the outcome at 2 years. From equation (2) one can see that for a fixed sample size power is inversely related to σ^2 and increases with ρ.

To provide realistic power projections, we used data from ADNI for parameter estimates. Specifically, we considered a moment-based estimator of ρ using a continuous autoregressive covariance model and σ^2 using the sample variance of the outcome at 2 years. The observed distribution of responses in ADNI indicate that power estimates based upon these parameter estimates accurately reflect the power afforded by application of the ANCOVA model in prospectively designed trials. We also calculated 95% confidence intervals for the variance and within-subject correlation using bootstrapping to further inform the level of precision expected to be obtained for each sample size and inclusion criteria scenario.

A natural question in this setting is whether model assumptions would hold in practice. We used residuals from an ANCOVA model fit to cerebrospinal fluid measures of total and phosphorylated tau from ADNI to assess the normality and homoscedasticity assumptions. These data suggest that residuals from an ANCOVA model fit to the tau responses would have slightly heavier tails, but we did not observe a gross departure from normality. By the Lindeberg-Feller Central Limit Theorem,[31] however, the distribution of the coefficient estimates from an ANCOVA model will still be approximately normally distributed. In addition, some heteroscedasticity of the residuals was observed. For the purposes of the power analysis, we provide a variance estimate marginalized over all residuals in order to provide readers the ability to utilize an analytic estimate of power. Use of the marginal variance results in little power discrepancy relative to the use of a robust variance estimator to account for heteroscedasticity in practice.

Results

Of the 1040 ADNI participants with a baseline diagnosis of mild cognitive impairment, 350 participants had at least two cerebrospinal fluid measurements, and 292 participants met at least one of the incorporated prodromal AD eligibility criteria. Table 1 presents the baseline demographics of participants in our study satisfying each of the biomarker eligibility criteria. The various criteria were associated with differing rates of inclusion;[23] specifically, fewer participants met high total tau criteria than the remaining biomarker criteria. Baseline characteristics of eligible participants were relatively similar, regardless of the biomarker criteria used.

We first estimated the 2-year variance and within-subject correlation for trials incorporating each of the biomarker eligibility criteria and cerebrospinal fluid phosphorylated tau as the primary outcome. We found that among the single eligibility criteria, the lowest variance (774.06, 95% confidence interval, CI: 586.60, 1020.52) was obtained if phosphorylated tau was used as the sole biomarker inclusion criterion. The highest 2-year within-subject correlation was obtained when Aβ was used as acceptable inclusion criterion (0.45, 95% CI: 0.35, 0.56).

Figure 1 presents the power curves and difference in power (compared to Aβ) for a total sample size of 50 (25 participants per arm) when amyloid beta, total tau, and phosphorylated tau were used as biomarker eligibility criteria. It should be noted that while we

Table 1. Baseline demographics of all participants who were eligible based on biomarker criteria.

	Aβ⩽192 pg/mL	t-tau > 93 pg/mL	p-tau > 23 pg/mL	Aβ⩽ 192 pg/mL or p-tau > 23 pg/mL	Aβ⩽ 192 pg/mL or p-tau/ Aβ > 0.10 pg/mL
N	243	141	263	288	286
Age (years)					
50–65	28 (11.52)	15 (10.64)	41 (15.59)	44 (15.28)	44 (15.38)
65–80	178 (73.25)	101 (71.63)	180 (68.44)	200 (69.44)	198 (69.23)
80–95	37 (15.23)	25 (17.73)	42 (15.97)	44 (15.28)	44 (15.38)
Gender					
Male	147 (60.49)	74 (52.48)	152 (57.79)	169 (58.68)	169 (59.09)
Female	96 (39.51)	67 (47.52)	111 (42.21)	119 (41.32)	117 (40.91)
Education					
0–12	37 (15.23)	22 (15.60)	38 (14.45)	43 (14.93)	43 (15.03)
13–16	89 (36.63)	54 (38.30)	92 (34.98)	99 (34.38)	101 (35.31)
16–20	108 (44.44)	60 (42.55)	122 (46.39)	134 (46.53)	130 (45.45)
Missing	9 (3.70)	5 (3.55)	11 (4.18)	12 (4.17)	12 (4.20)
Race					
White	234 (96.30)	136 (96.45)	247 (93.92)	272 (94.44)	271 (94.76)
Black	4 (1.65)	3 (2.13)	6 (2.28)	6 (2.08)	6 (2.10)
Asian	1 (0.41)	1 (0.71)	4 (1.52)	4 (1.39)	4 (1.40)
Hawaiian/Other PI	0 (0.00)	0 (0.00)	1 (0.38)	1 (0.35)	1 (0.35)
More than one	4 (1.65)	1 (0.71)	5 (1.90)	5 (1.74)	4 (1.40)
Ethnicity					
Not Hispanic/Latino	237 (97.53)	139 (98.58)	258 (98.10)	281 (97.57)	279 (97.55)
Hispanic/Latino	4 (1.65)	2 (1.42)	3 (1.14)	5 (1.74)	5 (1.75)
Unknown	2 (0.82)	0 (0.00)	2 (0.76)	2 (0.69)	2 (0.70)
Marital status					
Married	203 (83.54)	114 (80.85)	212 (80.61)	233 (80.90)	232 (81.12)
Divorced	16 (6.58)	8 (5.67)	22 (8.37)	24 (8.33)	24 (8.39)
Widowed	20 (8.23)	18 (12.77)	23 (8.75)	25 (8.68)	25 (8.74)
Never married	4 (1.65)	1 (0.71)	6 (2.28)	6 (2.08)	5 (1.75)
APOE e4					
0	84 (34.57)	44 (31.21)	103 (39.16)	115 (39.93)	112 (39.16)
1	118 (48.56)	75 (53.19)	124 (47.15)	132 (45.83)	133 (46.50)
2	41 (16.87)	22 (15.60)	36 (13.69)	41 (14.24)	41 (14.34)
MMSE	27.27 (1.82)	27.12 (1.76)	27.34 (1.88)	27.39 (1.86)	27.38 (1.86)
Amyloid beta (pg/mL)	137.33 (24.54)	138.29 (32.23)	153.21 (44.58)	152.66 (43.27)	150.98 (40.46)
Phosphorylated tau (pg/mL)	46.05 (22.33)	53.78 (21.83)	46.40 (20.68)	43.96 (21.31)	44.05 (21.37)
Total tau (pg/mL)	112.23 (55.56)	146.48 (49.17)	111.09 (53.23)	106.02 (53.77)	106.08 (53.98)

Aβ: amyloid beta; t-tau: total tau; p-tau: phosphorylated tau; PI: Pacific Islander; MMSE: Mini Mental State Examination; APOE: apolipoprotein E.

consider a total sample size of 50 participants, the shape of the power curves and the relative ordering remains the same when different sample sizes are used. Calculating power using the estimates of the variance and within-subject correlation, we found that the highest power was observed when phosphorylated tau was used as the biomarker inclusion criterion. Power also increased when we relaxed the eligibility criteria to include individuals meeting either low amyloid beta or high phosphorylated tau to amyloid beta ratio criteria. The minimum detectable treatment effect for 90% power was −33.950 pg/mL when amyloid beta was used as the sole eligibility criterion. The minimum detectable treatment effect was −32.065 pg/mL when restricting to participants with either low amyloid beta or high phosphorylated tau and −32.450 pg/mL when requiring either low amyloid beta or high phosphorylated tau to amyloid beta ratio (Table 2).

When power was considered for a primary outcome of change in cerebrospinal fluid total tau, the lowest variance among the single eligibility criteria was also observed when phosphorylated tau was used as the biomarker inclusion criterion (3249.15, 95% CI: 2217.82, 4386.21). If total tau was used as the inclusion criterion, the variance was estimated to be 3286.06 (95% CI: 2168.93, 4592.07). The highest within-subject correlation was observed when amyloid beta was used as the eligibility criterion (0.82, 95% CI: .77, 0.87), although the estimate was very similar to that when phosphorylated tau was used as the eligibility criterion (0.81, 95% CI: 0.76, 0.86). Within-subject correlation increased and variance decreased when the eligibility criteria were

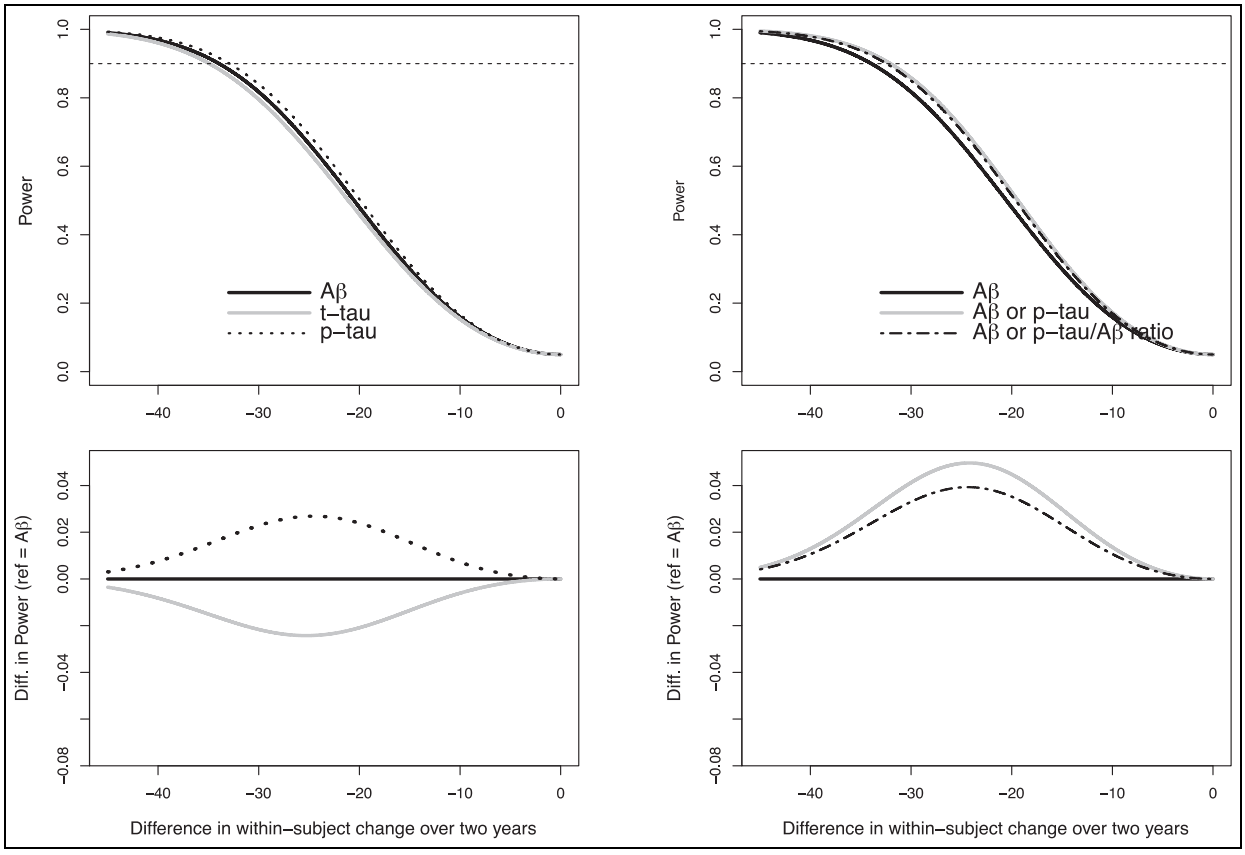

Figure 1. Power curves (top row) and difference in power compared to amyloid beta (Aβ) eligibility criterion (bottom row) for a sample size of 50 (with 25 participants per arm) using phosphorylated tau (p-tau) as the primary outcome. Single eligibility criteria are presented on the left column and multiple criteria are presented on the right column.

Table 2. Two-year variance, within-subject correlation, and minimum detectable difference (90% power) for a treatment effect with different inclusion criteria.

Eligibility criteria	σ^2 (95% CI)	**ρ**(95%**CI**)	Min. det. treatment effect
Phosphorylated tau outcome			
Amyloid beta	856.54 (629.82, 1133.37)	0.4469 (0.3516, 0.5612)	−33.950
Total tau	877.24 (611.07, 1206.67)	0.4168 (0.2626, 0.5787)	−34.910
Phosphorylated tau	774.06 (586.60, 1020.52)	0.4093 (0.2940, 0.5395)	−32.915
Amyloid beta or phosphorylated tau	772.65 (596.15, 1016.79)	0.4568 (0.3600, 0.5565)	−32.065
Amyloid beta or phosphorylated tau ratio	781.61 (597.59, 1001.62)	0.4460 (0.3558, 0.5546)	−32.450
Total tau outcome			
Amyloid beta	3602.46 (2447.07, 4805.04)	0.8187 (0.7744, 0.8653)	−44.695
Total tau	3286.06 (2168.93, 4592.07)	0.7125 (0.6118, 0.7832)	−52.155
Phosphorylated tau	3249.15 (2217.82, 4386.21)	0.8127 (0.7641, 0.8562)	−43.070
Amyloid beta or phosphorylated tau	3237.84 (2407.66, 4194.00)	0.8261 (0.7848, 0.8638)	−41.580
Amyloid beta or phosphorylated tau ratio	3286.73 (2429.27, 4362.66)	0.8256 (0.7894, 0.8722)	−41.950

CI: confidence interval.

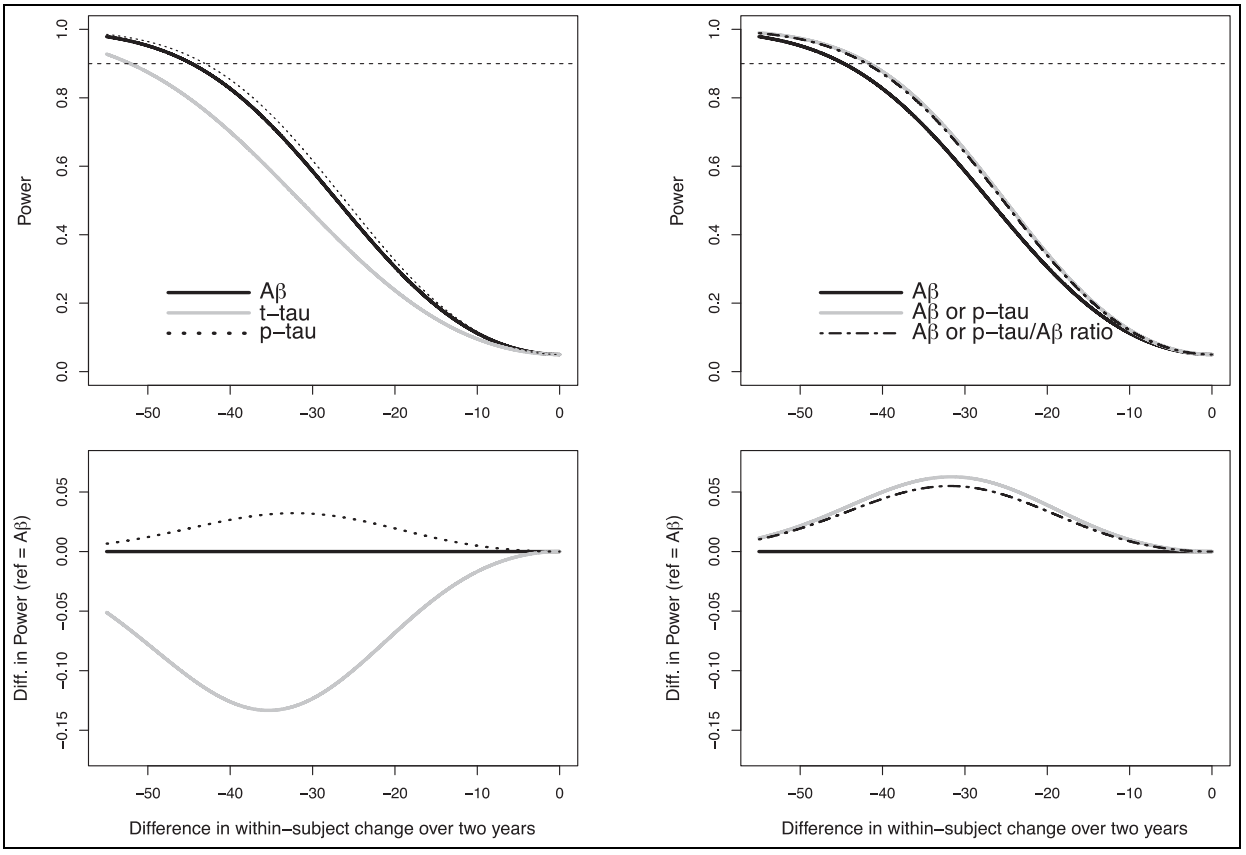

Figure 2. Power curves (top row) and difference in power compared to amyloid beta (Aβ) eligibility criterion (bottom row) for a sample size of 50 (with 25 participants per arm) using total tau (t-tau) as the primary outcome. Single eligibility criteria are presented on the left column and multiple criteria are presented on the right column.

broadened to allow enrollment of subjects with either low amyloid beta or high phosphorylated tau. The minimum detectable treatment effect was −44.695, −41.580, and −41.950 pg/mL for amyloid beta, amyloid beta or phosphorylated tau, and amyloid beta or phosphorylated tau to amyloid beta ratio, respectively (Figure 2).

Discussion

AD drug development is daunting.[32] Clinical trials for AD face numerous challenges. For example, AD trial recruitment has been described as a crisis.[33] On average, recruitment alone takes 157 weeks for efficacy trials of potential disease-modifying therapies.[34] This observation highlights the importance of effective learn-and-confirm approaches to AD drug development.[35] It is essential to make correct decisions early in the development process so that valuable resources are used only for the most promising treatments. To do this, trials must be designed carefully and ensure that proper outcomes are used, for example, as recommended by the Alzheimer's Drug Discovery Foundation and the Association for Frontotemporal Degeneration.[36] This in itself is a difficult task because complete understanding of disease pathophysiology and determination of the correct therapeutic targets remain areas of active investigation. Numerous lines of evidence point to neurofibrillary tangles as ideal therapeutic targets. Moreover, cerebrospinal fluid levels of phosphorylated and total tau, which are hypothesized to correlate with brain neurofibrillary tangle burden and neurodegeneration, respectively, may provide suitable outcome measures for trials of anti-tau therapies as well as other candidate strategies to slow AD progression.[37] Yet, few data are available to aid investigators designing trials with cerebrospinal fluid tau measures as primary outcomes. Our manuscript provides empirical estimates of the statistical properties of these biomarkers for different eligibility criteria to aid trial design in these settings.

We found that proof-of-concept phase 2 prodromal AD trials using phosphorylated tau as the primary outcome had the lowest variance when also incorporating phosphorylated tau as part of the inclusion criteria. This was expected because by enrolling only participants with high levels of phosphorylated tau at

baseline, trials also likely restrict levels of phosphorylated tau later in time, thereby leading to lower response variation. Following the same logic, we expected that if the primary outcome of the study was total tau, we would observe the lowest variance when total tau was part of the inclusion criteria. The lowest variance for trials using total tau as an outcome was, however, also obtained when phosphorylated tau was used as an inclusion criterion. This observation is likely due to the fact that total tau is a less specific biomarker for AD than is phosphorylated tau.[5,15,38] This decreased variability led to higher power when phosphorylated tau was applied as part of the inclusion criteria, regardless of whether the outcome was total tau or phosphorylated tau. This was the case even when the eligibility criteria were relaxed to allow participants to enroll either based on low amyloid beta or high phosphorylated tau.

While it is important to consider power and the efficient use of resources when designing phase 2 trials, it is also important to consider other factors such as the target population and generalizability of results. The outcome of interest must also be selected to provide insight into drug mechanism.[39] When biomarkers are used as the primary outcome, it is important to ensure that changes in levels of the biomarker represent clinically meaningful outcomes. Ultimately, this will be tested in later phase studies, examining clinical outcomes such as cognitive and functional performance or rates of progression to dementia. In this study, there were no differences in rates of progression to dementia between the differing inclusion criteria (data not shown).

From a population perspective, cerebrospinal fluid phosphorylated and total tau levels appear largely stable in mild-to-moderate dementia,[40–43] though at least some studies have found that cerebrospinal fluid total tau levels increase with disease progression.[44] In ADNI, the data source for the current study, longitudinal increases in phosphorylated tau (across diagnostic populations) were dependent upon having an AD biomarker signature (low cerebrospinal fluid amyloid beta) at baseline.[45] While these studies indicate potentially significant inter-individual longitudinal changes in cerebrospinal fluid outcomes, few[43] have provided information about statistical properties such as the variance and within-subject correlation of changes in cerebrospinal fluid tau. Although we present empirical estimates of the variance and within-subject correlation that can be used to estimate the power for studies with specific eligibility criteria, more data are needed to elucidate the optimal approach for powering proof-of-concept anti-tau therapy trials. Most notably, whether trials should be powered to reduce tau relative to baseline versus reducing change over time remains an open area of study. Here, power appeared contingent upon interventions that can reduce baseline tau levels.

Neurofibrillary tangles can now be measured through positron emission tomography imaging.[46] The use of tau positron emission tomography may also facilitate proof-of-concept trials by providing evidence of target engagement.[47] Measures of tau positron emission tomography correlate with cerebrospinal fluid phosphorylated tau[48] but have the added benefit of providing regional deposition information and visual measures of pathological spreading over time. A recent study using data from ADNI, however, found that baseline levels of cerebrospinal fluid phosphorylated tau (dichotomized as elevated or not elevated based on a slightly higher threshold than that used in this study (26 vs 23 pg/mL)) is a better predictor of changes in phosphorylated tau over time, compared to tau positron emission tomography imaging.[49] Discordance between cerebrospinal fluid phosphorylated tau and tau positron emission tomography was also more frequently characterized by abnormal cerebrospinal fluid phosphorylated tau and normal tau positron emission tomography than vice versa. This may suggest that cerebrospinal fluid phosphorylated tau provides greater sensitivity in early disease, compared to tau positron emission tomography. Another recent study suggests that the relationship between cerebrospinal fluid tau and positron emission tomography may depend on the degree of neurodegeneration,[50] highlighting additional benefits of the use of positron emission tomography. Trials incorporating tau positron emission tomography, however, might require additional scans to assess amyloid status, or would need to incorporate cerebrospinal fluid as well, which offers single measure information on amyloid beta, total tau, and phosphorylated tau, as well as other potentially useful markers.[51]

Limitations

ADNI is a large and widely used data source that is known to have significant sample bias—participants are overwhelmingly white and highly educated. This bias was likely exacerbated in the current study, which was limited to data from participants who had at least two cerebrospinal fluid measurements available. In fact, relative to previous studies,[23] we note that a greater proportion included here met AD cerebrospinal fluid biomarker criteria. It should be noted that the estimates provided may not be appropriate for studies with very different patient populations. Nevertheless, the characteristics of participants in this sample are similar to those of prodromal AD trial participants and will therefore be helpful in designing most studies. When determining study eligibility, we only considered one threshold for each biomarker, but there are currently no universally agreed-upon cutoffs[4,52] and thresholds may in fact need to differ for unique populations.[53]

Similarly, we considered a single assay. Whether these results would differ if different assays and thresholds were used is unknown. The number of cerebrospinal fluid samples was limited for some of our scenarios, and as expected there was attrition in sample number over time. Small sample number may explain some of the counterintuitive findings in this study, such as reduced variance with broader inclusion criteria, though this will require further study. Finally, we considered a 2-year trial. It is unknown whether and how statistical characteristics would differ for longer studies, and how this would impact power for different eligibility criteria.

Conclusion

Phase 2 proof-of-concept studies are essential to instruct logical and efficient drug development. High type 1 errors in these studies risk wasted precious resources in larger later phase studies, while high type 2 errors risk terminated development of potentially effective therapies. This study not only provides empirical estimates of variation of commonly used biomarker responses in early-phase AD trials to aid in informed study design but also suggests that incorporating phosphorylated tau as part of the inclusion criteria in phase 2 proof-of-concept studies with tau as an outcome could help reduce variance and improve power, lowering risk of failed trials or incorrect conclusions.

Authors' note

*Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: J.D.G. has consulted for SiteRx. The remaining authors declare that they have no conflict of interest.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: M.M.N. was supported by the National Science Foundation Graduate Research Fellowship (grant no. DGE-1321846). J.D.G. and D.L.G. were supported by NIA AG016573, NIA AG066519, NIA AG059407, and UC Cures Alzheimer's BRD-16-501350. J.D.G. was supported by NIH UL1 TR000153. Any opinions, findings, and conclusions or recommendations expressed in this material are those of the authors and do not necessarily reflect the views of the National Science Foundation or the National Institutes of Health. Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California.

ORCID iD

Michelle M Nuño https://orcid.org/0000-0003-2031-929X
Joshua D Grill https://orcid.org/0000-0002-4215-7589

References

1. National Institute on Aging. Basics of Alzheimer's disease and dementia: What is Alzheimer's Disease? https://www.nia.nih.gov/health/what-alzheimers-disease (2017, accessed 3 March 2021).
2. Patterson C. The state of the art of dementia research: new frontiers, 2018, https://www.alzint.org/u/WorldAlzheimerReport2018.pdf
3. Cummings J, Feldman HH and Scheltens P. The "rights" of precision drug development for Alzheimer's disease. *Alzheimers Res Ther* 2019; 11: 76.
4. Jack CR, Bennett DA, Blennow K, et al. A/T/N: an unbiased descriptive classification scheme for Alzheimer disease biomarkers. *Neurology* 2016; 87: 539–547.
5. La Joie R, Bejanin A, Fagan AM, et al. Associations between [18F] AV1451 tau PET and CSF measures of tau pathology in a clinical sample. *Neurology* 2018; 90: e282–e290.
6. Jack CR, Wiste HJ, Lesnick TG, et al. Brain beta-amyloid load approaches a plateau. *Neurology* 2013; 80: 890–896.

7. Arriagada PV, Growdon JH, Hedley-Whyt ET, et al. Neurofibrillary tangles but not senile plaques parallel duration and severity of Alzheimer's disease. *Neurology* 1992; 42: 631–639.
8. Nelson PT, Alafuzoff I, Bigio EH, et al. Correlation of Alzheimer disease neuropathologic changes with cognitive status: a review of the literature. *J Neuropathol Exp Neurol* 2012; 71(5): 362–381.
9. Bejanin A, Schonhaut DR, La Joie R, et al. Tau pathology and neurodegeneration contribute to cognitive impairment in Alzheimer's disease. *Brain* 2017; 140: 3286–3300.
10. Ossenkoppele R, Smith R, Ohlsson T, et al. Associations between tau, Abeta, and cortical thickness with cognition in Alzheimer disease. *Neurology* 2019; 92: e601–e612.
11. Pradeepkiran JA, Reddy AP and Reddy PH. Pharmacophore-based models for therapeutic drugs against phosphorylated tau in Alzheimer's disease. *Drug Discov Today* 2019; 24(2): 616–623.
12. Chong FP, Ng KY, Koh RY, et al. Tau proteins and tauopathies in Alzheimer's disease. *Cell Mol Neurobiol* 2018; 38(5): 965–980.
13. Hansson O, Zetterberg H, Buchhave P, et al. Association between CSF biomarkers and incipient Alzheimer's disease in patients with mild cognitive impairment: a follow-up study. *Lancet Neurol* 2006; 5(3): 228–234.
14. Andreasen N, Vanmechelen E, Vanderstichele H, et al. Cerebrospinal fluid levels of total-tau, phospho-tau and Abeta-42 predicts development of Alzheimer's disease in patients with mild cognitive impairment. *Acta Neurol Scand Suppl* 2003; 179: 47–51.
15. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the national institute on aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011; 7(3): 270–279.
16. Dubois B, Feldman HH, Jacova C, et al. Revising the definition of Alzheimer's disease: a new lexicon. *Lancet Neurol* 2010; 9(11): 1118–1127.
17. Cummings JL, Dubois B, Molinuevo JL, et al. International Work Group criteria for the diagnosis of Alzheimer disease. *Med Clin North Am* 2013; 97(3): 363–368.
18. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Focus* 2013; 11: 96–106.
19. Coric V, Salloway S, van Dyck CH, et al. Targeting prodromal Alzheimer disease with avagacestat: a randomized clinical trial. *JAMA Neurol* 2015; 72(11): 1324–1333.
20. Egan MF, Kost J, Tariot PN, et al. Randomized trial of verubecestat for mild-to-moderate Alzheimer's disease. *N Engl J Med* 2018; 378: 1691–1703.
21. Ostrowitzki S, Lasser RA, Dorflinger E, et al. A phase III randomized trial of gantenerumab in prodromal Alzheimer's disease. *Alzheimers Res Ther* 2017; 9: 95.
22. Frolich L, Ashwood T, Nilsson J, et al. Effects of AZD3480 on cognition in patients with mild-to-moderate Alzheimer's disease: a phase IIb dose-finding study. *J Alzheimers Dis* 2011; 24(2): 363–374.
23. Grill JD, Nuño MM, Gillen DL, et al. Which MCI patients should be included in Prodromal Alzheimer Disease Clinical Trials. *Alzheimer Dis Assoc Disord* 2019; 33(2): 104–112.
24. Congdon EE and Sigurdsson EM. Tau-targeting therapies for Alzheimer disease. *Nat Rev Neurol* 2018; 14(7): 399–415.
25. Nicotinamide as an Early Alzheimer's Disease Treatment, https://ClinicalTrials.gov/show/NCT03061474
26. Study of LY2886721 in mild cognitive impairment due to Alzheimer's Disease or Mild Alzheimer's Disease, https://ClinicalTrials.gov/show/NCT01561430
27. Petersen RC, Smith GE, Waring SC, et al. Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol* 1999; 56(3): 303–308.
28. Initiative AsDN. ''Study Design''. Alzheimer's Disease Neuroimaging Initiative, http://adni.loni.usc.edu/study-design/ (2017, accessed 22 April 2020).
29. Shaw LM, Vanderstichele H, Knapik-Czajka M, et al. Cerebrospinal fluid biomarker signature in Alzheimer's disease neuroimaging initiative subjects. *Ann Neurol* 2009; 65: 403–413.
30. Fitzmaurice GM, Laird NM and Ware JH. *Applied longitudinal analysis*. Hoboken, NJ: John Wiley & Sons, 2012.
31. Lindeberg JW. Eine neue Herleitung des Exponentialgesetzes in der Wahrscheinlichkeitsrechnung. *Mathematische Zeitschrift* 1922; 15: 211–225.
32. Cummings JL, Morstorf T and Zhong K. Alzheimer's disease drug-development pipeline: few candidates, frequent failures. *Alzheimers Res Ther* 2014; 6(4): 37.
33. Fargo KN, Carrillo MC, Weiner MW, et al. The crisis in recruitment for clinical trials in Alzheimer's and dementia: an action plan for solutions. *Alzheimers Dement* 2016; 12(11): 1113–1115.
34. Cummings J, Lee G, Ritter A, et al. Alzheimer's disease drug development pipeline: 2019. *Alzheimers Dement* 2019; 5: 272–293.
35. Gray JA, Fleet D and Winblad B. The need for thorough phase II studies in medicines development for Alzheimer's disease. *Alzheimers Res Ther* 2015; 7: 67.
36. Friedman LG, McKeehan N, Hara Y, et al. Value-generating exploratory trials in neurodegenerative dementias. *Neurology* 2021; 96: 944–954.
37. Iqbal K, Liu F and Gong CX. Tau and neurodegenerative disease: the story so far. *Nat Rev Neurol* 2016; 12(1): 15–27.
38. Andreasen N, Sjögren M and Blennow K. CSF markers for Alzheimer's disease: Total tau, phospho-tau and Aβ42. *World J Biol Psychiatry* 2009; 4: 147–155.
39. Greenberg BD, Carrillo MC, Ryan JM, et al. Improving Alzheimer's disease phase II clinical trials. *Alzheimers Dement* 2013; 9(1): 39–49.
40. Sunderland T, Wolozin B, Galasko D, et al. Longitudinal stability of CSF tau levels in Alzheimer patients. *Biol Psychiatry* 1999; 46: 750–755.
41. Blennow K, Zetterberg H, Minthon L, et al. Longitudinal stability of CSF biomarkers in Alzheimer's disease. *Neurosci Lett* 2007; 419: 18–22.

42. Le Bastard N, Aerts L, Sleegers K, et al. Longitudinal stability of cerebrospinal fluid biomarker levels: fulfilled requirement for pharmacodynamic markers in Alzheimer's disease. *J Alzheimers Dis* 2013; 33(3): 807–822.
43. Zetterberg H, Pedersen M, Lind K, et al. Intra-individual stability of CSF biomarkers for Alzheimer's disease over two years. *J Alzheimers Dis* 2007; 12(3): 255–260.
44. Buchhave P, Blennow K, Zetterberg H, et al. Longitudinal study of CSF biomarkers in patients with Alzheimer's disease. *PLoS ONE* 2009; 4: e6294.
45. Toledo JB, Xie SX, Trojanowski JQ, et al. Longitudinal change in CSF Tau and Aβ biomarkers for up to 48 months in ADNI. *Acta Neurophatol* 2013; 126: 659–670.
46. Ossenkoppele R, Rabinovici GD, Smith R, et al. Discriminative accuracy of [18F] flortaucipir positron emission tomography for Alzheimer disease vs other neurodegenerative disorders. *JAMA* 2018; 320: 1151–1162.
47. Brosch JR, Farlow MR, Risacher SL, et al. Tau imaging in Alzheimer's disease diagnosis and clinical trials. *Neurotherapeutics* 2017; 14(1): 62–68.
48. Brier MR, Gordon B, Friedrichsen K, et al. Tau and Abeta imaging, CSF measures, and cognition in Alzheimer's disease. *Sci Transl Med* 2016; 8: 338ra66.
49. Meyer P-F, Binette AP, Gonneaud J, et al. Characterization of Alzheimer disease biomarker discrepancies using cerebrospinal fluid phosphorylated tau and AV1451 positron emission tomography. *JAMA Neurol* 2020; 77: 508–516.
50. Leuzy A, Cicognola C, Chiotis K, et al. Longitudinal tau and metabolic PET imaging in relation to novel CSF tau measures in Alzheimer's disease. *Eur J Nucl Med Mol Imaging* 2019; 46(5): 1152–1163.
51. Wellington H, Paterson RW, Portelius E, et al. Increased CSF neurogranin concentration is specific to Alzheimer disease. *Neurology* 2016; 86: 829–835.
52. Jack CR Jr, Knopman DS, Chetelat G, et al. Suspected non-Alzheimer disease pathophysiology—concept and controversy. *Nat Rev Neurol* 2016; 12(2): 117–124.
53. Garrett SL, McDaniel D, Obideen M, et al. Racial disparity in cerebrospinal fluid amyloid and tau biomarkers and associated cutoffs for mild cognitive impairment. *JAMA Netw Open* 2019; 2: e1917363.