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RESEARCH ARTICLE

Measuring time saved in Alzheimer's disease: What is a meaningful slowing of progression?

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Abstract

INTRODUCTION: Minimal clinically important differences (MCIDs) for Alzheimer's disease (AD) have previously been estimated using clinician-based anchors. However, MCIDs have been criticized for not reflecting the preferences of people living with AD (PLWAD). Furthermore, interpretations of clinical trial results have been criticized for conflating within-person meaningfulness thresholds and between-group differences. Here, we simulate scenarios of disease slowing and compare those to published MCIDs.

METHODS: Scenarios of 5%–95% disease slowing were simulated using Alzheimer's Disease Neuroimaging Initiative (ADNI) data. Time saved and point differences on the Clinical Dementia Rating scale—Sum of Boxes (CDR-SB) were estimated for these scenarios and compared to published MCIDs.

RESULTS: Scenario analyses resulted in estimates of time saved at ~3 weeks–17 months and mean changes at 0.08–1.5 CDR-SB points over 18 months. The often referenced MCID for mild cognitive impairment (0.98) thereby corresponded to 11 months slowing, whereas the MCID for mild dementia (1.63) corresponded to >17 months slowing.

DISCUSSION: Translating trial endpoints to estimates of time saved supports that often-referenced MCIDs may not be aligned with realistic and meaningful slowing of clinical progression.

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KEYWORDS
ADNI data, Alzheimer's disease, Clinical Dementia Rating scale—Sum of the Boxes, meaningful within-person change, minimal clinically important difference, patient perspective, PLWAD

Highlights

- AD slowing of clinical progression by 5%–95% resulted in 0.74–17 months saved and 0.08–1.5 CDR-SB points change at 18 months.
- Slowing of at least 60% or 11 months of time saved over 18 months met an often-cited MCID threshold of 0.98 points for mild cognitive impairment.
- For mild AD dementia, an MCID of 1.63 meant that even an 18-month delay over 18 months would be considered only borderline meaningful—a face invalid and unrealistic proposition.

1 | BACKGROUND

Alzheimer's disease (AD) is a debilitating neurodegenerative disorder causing enormous distress and burden for people living with AD (PLWAD), their families and society as a whole.[1–3] Previously, management was limited to symptomatic drugs used in combination with non-pharmacological approaches to care.[4–7] Several amyloid plaque-lowering monoclonal antibody (APLmAb) drugs in clinical trials of early AD (mild cognitive impairment [MCI] due to AD and mild AD dementia) have demonstrated amyloid-plaque lowering and beneficial effects on cognitive and functional endpoints at 18 months.[8–11] These results provide the support that some APLmAbs may be considered disease modifying treatments (DMTs)[12] and that the group-level treatment effects observed in clinical trials can translate to and provide a foundation to further build on for meaningful benefits for PLWAD and their families.[13–18] However, others have questioned the clinical meaningfulness of the observed treatment effects on these clinical trial outcomes.[19,20]

In this context, the concept of minimal clinically important difference (MCID), also known as minimal important difference or minimal clinically relevant change, has gained attention in the Alzheimer´s field.[21,22] The MCID can be defined as "the smallest difference in score in the domain of interest which patients perceive as beneficial".[23] Several studies have tried to estimate within-patient MCIDs for common primary outcomes in AD trials, for example, 3–4 points on the 11-item Alzheimer's Disease Assessment Scale—Cognitive subscale (ADAS-cog) over 6 months[24] and more recently about 1–2 points on the Clinical Dementia Rating scale—Sum of Boxes (CDR-SB) over 12 months depending on the stage of disease.[25,26] However, limitations of these proposed MCIDs and studies have been highlighted,[14,27,28] in parallel with discussions on the theoretical underpinnings of the concept of MCID and its measurement.[14,29] The main critiques are threefold. First, while the definition of MCID centers on changes "which the patients perceive," the referenced studies all used clinician-reported anchors to determine meaningful change for an individual PLWAD, with no consideration of patient preferences. Second, the studies report analyses of within-patient MCIDs, that is, the MCID measuring the difference in scores between two visits of each PLWAD, while clinical trials report mean changes between entire groups, that is, the difference in average scores between two visits of a group of PLWAD or two groups at the same time point, which may be different from individual-level changes.[14,28] Third, clinical scales like CDR-SB and ADAS-cog have different impacts and represent different types of abilities affected depending on what symptoms or losses of function they signify at any particular step on the scales.[30]

These critiques are particularly troublesome for any applications of such MCIDs when evaluating a between-group difference reported from clinical trials. They are not comparable, which may not be evident when considering effects on a complex measure such as CDR-SB. To put results in more patient-relevant terms, we may consider another representation of the same outcome: time saved, that is, the amount of additional time a patient would have before progression to another stage of disease. PLWAD do not use the vocabulary of clinical trial outcome measures or speak in terms of point changes on scales but rather they appreciate, value, and converse in terms of abilities (preserving them), the degree to which they are retained, and of time.[31,32] While time still measures between-group rather than within-person changes, comparing the trial arms on a time scale allows for quantification of the average treatment effect in terms of a delay or slowing of progression at certain points in time, which is also called "time saved" with treatment. The "time saved" approach is face valid and may better clarify, compared to a difference in points on a clinical trial outcome scale, to PLWAD and their care partners the effect of a DMT in slowing the cognitive or functional loss in terms of the time (i.e., months or years). It may also be more clinically interpretable to clinicians than assessing changes in clinical outcome scores. Additionally, it may facilitate comparisons across trials that use different outcome measures by standardizing time as a common metric in these analyses.[15,33–38]

The current project assessed how different evidence-based scenarios for slowing disease progression in early AD translated point differences in the CDR-SB into estimates of time saved. These

estimates were then compared to published MCIDs to assess the face validity of these proposed MCIDs.

2 | METHODS

2.1 | Study design and study population

To simulate the conditions of a placebo arm in an interventional trial, data were extracted from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu),[39] including participants who met typical inclusion criteria of DMT clinical trials in early AD (Table 1[40]).

Launched in 2003 as a public-private partnership under the leadership of Principal Investigator Michael W. Weiner, MD, ADNI aims to explore whether serial magnetic resonance imaging, positron emission tomography, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of early stages of AD. The current objectives include validating biomarkers for clinical trials, enhancing the diversity of the participant cohort to improve the generalizability of ADNI data, and providing valuable data concerning the diagnosis and progression of AD to the scientific community. For up-to-date information, see adni.loni.usc.edu.

2.2 | Analysis of ADNI data with simulated treatment effects

Analysis of ADNI data followed a stepwise process similar to Jonsson et al. (Table 2).[38,41] Steps 2 through 5 were repeated 1000 times, and the mean and the 2.5th and 97.5th percentiles of the simulated scenarios are reported as the mean and limits for 95% confidence intervals.

2.3 | External validation with data from APLmAb clinical trials

To provide context for the results simulated with ADNI data, we extracted baseline scores and trajectories of change in CDR-SB scores from the placebo-arms of six published clinical trials involving APLmAb DMTs. The trials assessed were CLARITY AD with lecanemab,[42] TRAILBLAZER-ALZ 2 (both the full population and low-medium *Tau* subgroup) with donanemab,[11] EMERGE and ENGAGE with aducanumab,[43–45] and GRADUATE I and II with gantenerumab.[46] It should be noted that because EMERGE and ENGAGE studies were terminated prematurely for futility, the estimated placebo decline

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using traditional (e.g., PubMed) sources. There are a few published minimal clinically important differences (MCIDs) suggested to be used to determine the clinical meaningfulness of the treatment effects reported from Alzheimer's disease (AD) clinical trials. However, they have been criticized for misapplying between-group differences to within-person meaningfulness thresholds and for not representing the preferences of people living with AD (PLWAD).
2. **Interpretation**: Translating standard trial endpoints to the concept of "time saved" from a slowing of disease progression shows that published MCIDs are misaligned with expected benefits of disease-modifying treatments in the mild cognitive impairment (MCI) and mild dementia stages of AD (aka early symptomatic/early AD). When misapplying such published MCID definitions, even a complete halt of clinical progression in early AD would only be considered borderline meaningful at 18 months and would lead to conclusions that are not face valid.
3. **Future directions**: The preferences of PLWAD should be central to any assessment of what is considered clinically meaningful. Between-group differences observed in clinical trials should not be misinterpreted in the context of within-person meaningfulness thresholds. PLWAD should be involved in future research aimed at developing new MCIDs to better guide the assessments on which interventions are meaningful in AD.

TABLE 1 Inclusion criteria for ADNI cohort

Inclusion criteria	Details
Age	55–85 years
Amyloid status	Amyloid positive by positron emission tomography scan or a cerebrospinal fluid analysis
Clinical diagnosis	MCI or mild dementia due to AD
Mini-Mental State Examination score[40]	≥22
CDR global score	0.5, with ≥0.5 in at least one of the three instrumental activities of daily living categories (personal care, home and hobbies, community affairs) or a CDR global score of 1.0 at baseline

Abbreviations: AD, Alzheimer's disease; ADNI, Alzheimer's Disease Neuroimaging Initiative; CDR, Clinical Dementia Rating; MCI, mild cognitive impairment.

TABLE 2 Analysis of simulated ADNI data

Step number	Step description	Details
1	Estimate placebo arm trajectories	CDR-SB scores at each visit (baseline, 6-, 12-, 18-, 24-, and 36-months post-baseline) were estimated using a constrained longitudinal data analysis model. This assumed an unconstructed covariance matrix (meaning no assumptions are made about the variances and covariances between individuals´ scores across visits)[41].
2	Simulate placebo-arm trajectory	The resulting model parameters and covariance matrix were used to simulate the trajectory of a hypothetical placebo-arm of 700 patients over 36 months.
3	Simulate treatment arm trajectories	Using the same model (as in Step 2), hypothetical treatment arm trajectories were simulated, introducing treatment effects slowing AD clinical progression by 5%–95%, measured by CDR-SB.
4	Fit PMRM model to estimate time saved	PMRM model was fitted to estimate the time saved at 18 and 24 months.
5	Fit MMRM model to estimate the difference in CDR-SB	MMRM model was used to estimate the difference in CDR-SB at 18 and 24 months.

Abbreviations: AD, Alzheimer's disease; ADNI, Alzheimer's Disease Neuroimaging Initiative; CDR-SB, Clinical Dementia Rating scale—Sum of the Boxes; MMRM, mixed model for repeated measures; PMRM, progression models for repeated measures.

rates are likely biased toward less decline than would have been evident if the studies had been completed. Once the 18-months placebo trajectories of change in CDR-SB were extracted for each trial, we estimated how much these treatments could slow down the disease by calculating time savings. Treatment effects resulting in a slowing of disease progression, as measured by CDR-SB, by 5%, 20%, 30%, 60%, and 95% over a period of 18 months were hypothesized and calculated by using linear interpolation. For instance, a slowing of 5% implied a 5% smaller increase in CDR-SB compared to the mean change in the placebo-arm, and the resulting time saving was derived by measuring the difference in time between the two trajectories at the same CDR-SB scores on the x-axis.

2.4 | Comparison of results with published MCIDs in AD

The point differences in CDR-SB estimated with ADNI simulated data and observed in AD APLmAb Phase 3 clinical trials at each time point were compared to suggested MCIDs in AD.[22,25] As noted above, the application of these clinician-anchored within-patient MCIDs to between-group differences reported from clinical trials has been criticized because they are not two comparable entities.[14,27,28] Still, because these MCIDs have been considered in the context of evaluating the meaningfulness of between-group differences reported from clinical trials,[47] perhaps in the absence of better evidence, it is important to put them side by side with our findings to test their face validity.

3 | RESULTS

In total, 423 participants in ADNI met the inclusion criteria for most typical DMT clinical trials (Figure S1). Compared to typical clinical trial participants, ADNI participants were more often male but of similar age and with comparable severity of symptoms at baseline, although trials showed notable variation (Table 3).

3.1 | Analysis of ADNI data

In the ADNI cohort, a hypothetical slowing of the disease in early AD by 5%–95% corresponded to a time saved of ~3 weeks to 17 months (0.74–16.96 months) after 18 months. This corresponded to a mean change of 0.08–1.46 points on CDR-SB. The corresponding time saved and mean change at 24 months were ~5 weeks to ~2 years (1.11–22.63 months) and 0.19–2.40 points, respectively (Figures 1 and S2).

3.2 | Comparison to published clinical trial data

Using Phase 3 APLmAb clinical trial data, a slowing of disease progression (as measured by CDR-SB) by 5%–95%, representing a saving of ~1 to ~17 months in disease progression at 18 months, corresponded to a point difference in CDR-SB of between 0.10 and 2.26 points at 18 months (Table 4, Figure S3). There was variability in the placebo decline observed across the trials (e.g., observed placebo decline rates resulted in differences of 1.47–2.26 points in CDR-SB when assuming a 95% slowing, compared to the 1.46 points obtained using the ADNI cohort as seen in Figure 1).

3.3 | Comparison of ADNI data with simulated treatment effects with published MCIDs

Notwithstanding the criticism outlined above, suggested published MCIDs in CDR-SB in early AD range between about 1 to 2 points up

TABLE 3 Comparison of baseline characteristics of ADNI cohort and amyloid plaque-lowering monoclonal antibody Phase 3 clinical trials

Parameter	Emulated ADNI cohort	CLARITY AD Lecanemab[42]	TRAILBLAZER-AZ 2 Donanemab[11]	EMERGE Aducanumab[43–45]	ENGAGE Aducanumab[43,45]	GRADUATE 1 Gantarenumab[46]	GRADUATE 2 Gantarenumab[46]
N	423	1734[a]	1736[c]	1638	1647	984[a]	975[a]
MCI, *n* (%)	244 (57.7)	1072 (61.85)	283 (16.3)	1336 (81.6)	1325 (80.4)	538 (54.6)	535 (54.9)
Male, *n* (%)	241 (57.0)	827 (47.7)	740 (42.6)	795 (48.5)	784 (47.6)	439 (44.6)	402 (41.2)
Age, years, mean (SD)	73 (7.3)	71 (50, 90)[b]	73.0 (6.2)	70.7 (7.4)	70.1 (7.5)	71.6 (7.8)	71.7 (7.6)
Baseline CDR-SB, mean (SD)	3.1 (1.5)	3.2 (1.3)[d]	3.95 (2.1)	2.5 (1.0)	2.4 (1.0)	3.7 (1.61)	3.6 (1.58)
Baseline MMSE, mean (SD)	26 (2.3)	25.6 (2.2)	22.3 (3.8)	26.3 (1.7)	26.4 (1.8)	23.6 (3.2)	23.7 (3.1)

Abbreviations: ADNI, Alzheimer's Disease Neuroimaging Initiative; CDR-SB, Clinical Dementia Rating scale—Sum of the Boxes; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination

[a]This is the total number of patients who were analyzed for baseline characteristics.

[b]Data presented as median (range).

[c]Combined population.

[d]For 1795 patients.

to 2.5 points,[26] where a lower MCID of 0.98 has been suggested for PLWAD with MCI and a higher of 1.63 for PLWAD with mild dementia (Figure 1).[25] Compared to our estimates, using the ADNI placebo decline rate and confirmed by similar clinical trial placebo decline rates, this implies that over 18 months, a slowing of at least 60% (~11 months of time saved out of 18 months) would be required for a treatment effect to be potentially considered meaningful in persons living with MCI. In mild AD dementia, not even 17 months of time saved (i.e., a 95% slowing or almost a complete halt of the disease) would be considered meaningful at 18 months if one were to accept the MCIDs above as necessary to achieve clinical meaningfulness.

4 | DISCUSSION

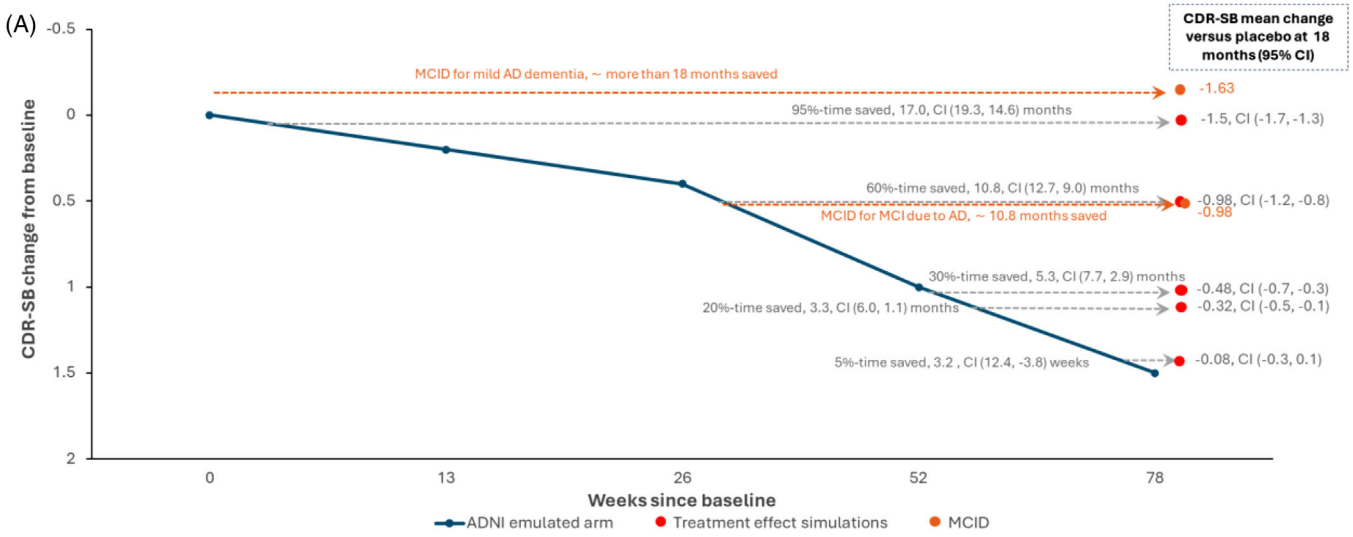
In our analysis, we estimated what a potential slowing of clinical progression in early symptomatic AD would translate to in terms of time saved and point differences on CDR-SB using different scenarios and modeling simulations. An often-referenced published MCID on CDR-SB for persons living with MCI due to AD is 0.98,[25] which our modeling analysis estimates would correspond to an 11-month delay over an 18-month period. Our results also show that for persons living with mild AD dementia, utilizing the suggested MCID on CDR-SB of 1.63[25] would imply that even a complete halt in clinical progression (i.e., an 18-month delay over 18 months) would only be considered borderline clinical meaningfulness. However, time saved of these magnitudes during early AD, including, theoretically, an essential halt in clinical progression over 18 months, would clearly have face validity for being clinically meaningful.

Soliciting preferences of PLWADs was not an objective of this study, but a draft version of the manuscript was shared for review with representatives of the Global Dementia Experts Panel (GDEP), including the Director of Research and Publications at Alzheimer's Disease International (ADI) along with three care partners and three people living with dementia (PLWD) in total, from Malaysia, the Maldives, Singapore, South Africa, the United Kingdom, and the United States. The group reviewed the findings of the study and unanimously agreed on the importance of time saved as a meaningful outcome for them. However, they emphasized that this time saved should be of good quality—positive and functional—rather than simply extending the duration of severe disease states. In other words, the value of time saved is enhanced when it is associated with a higher quality of life, which is observed in earlier-stage disease, rather than merely prolonging the length of time in a severely deteriorated condition. Their discussion did not allow for empirical quantification of what they considered a minimum amount of time saved in a non-severely advanced dementia stage that would be considered meaningful for them. Some statements supported the nuance, complexity, and subjective importance of what a delay or time saved could be considered meaningful, depending on context including individual preferences, age, and culture. This was evidenced in quotes like the following:

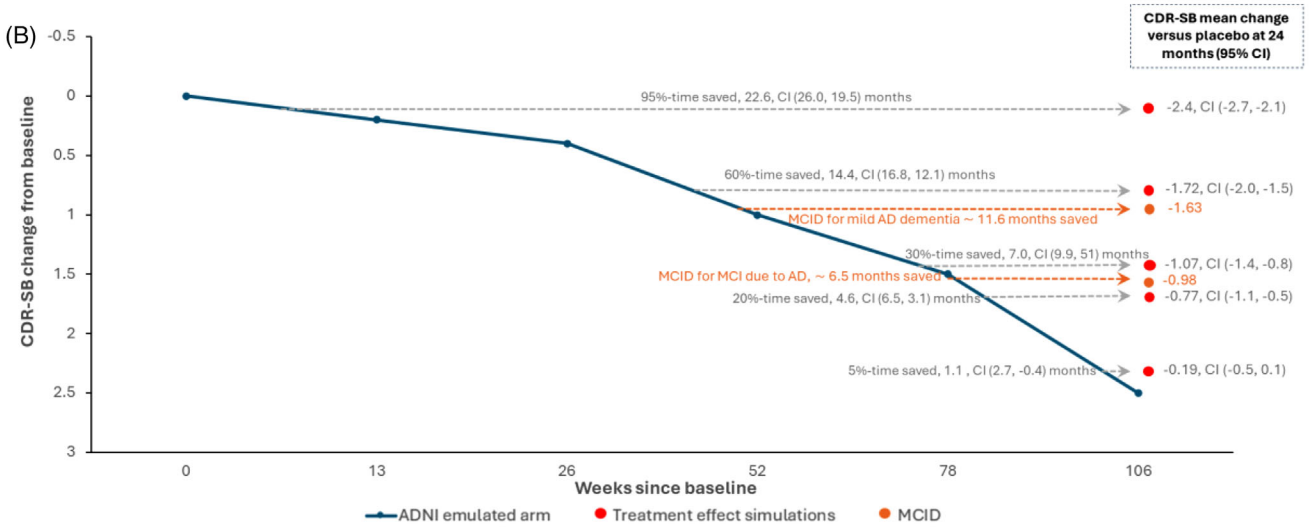
Care partner: "It's unethical to ask me meaningful delay. Well, any day, any month in a year is a meaningful delay for me to have, you know, to live my life without that disease, or with that disease managed in a better way."

Care partner: "First, let me just go back and say (something about) clinical meaningfulness. To a whole lot of South African patients, maybe more African patients, clinical meaningfulness in terms of time saved would be anything, even if it's a day."

With everything else being equal (e.g. potential side effects), a single day is better than nothing, yet anecdotal evidence suggests decision-makers and some clinicians set a bar that may be much higher including suggestions that anything less than 6 months of delay is not meaningful. For comparison, the time saved with lecanemab has been estimated



Abbreviations: MCID = Minimal Clinically Important Difference; CDR-SB = Clinical Dementia Rating Scale Sum of Boxes; MCI = Mild Cognitive Impairment; AD = Alzheimer's Disease, CI = 95% Confidence Interval



Abbreviations: MCID = Minimal Clinically Important Difference; CDR-SB = Clinical Dementia Rating Scale Sum of Boxes; MCI = Mild Cognitive Impairment; AD = Alzheimer's Disease, CI = 95% Confidence Interval

FIGURE 1 Simulated treatment effect at 18 months (A) and 24 months (B) assuming slowing of AD clinical progression between 5% and 95% based on ADNI data. Horizontal dotted lines show point estimates (mean and CI) for time-saved at levels of slowing in clinical progression achieved by treatment of 5%, 20%, 30%, 60%, and 95% (from bottom to top) of that of placebo progression. The orange dots and lines represent the MCIDs suggested for PLWAD with MCI (−0.98) and those with mild dementia (−1.63). Horizontal dotted lines show point estimates (mean and CI) for time-saved at levels of slowing in clinical progression achieved by treatment of 5%, 20%, 30%, 60%, and 95% (from bottom to top) of that of placebo progression. AD, Alzheimer's disease; ADNI, Alzheimer's Disease Neuroimaging Initiative; CI, confidence interval; MCI, mild cognitive impairment; MCIDs, Minimal clinically important differences.

at 24.3 weeks (or approximately 5.6 months) based on 18 months data from the CLARITY-AD trial and for donanemab at 30.1 weeks (or approximately 7 months) based on 18 months of data from the TRAILBLAZER-ALZ 2 trial.[8]

Understanding the PLWAD perspective on the meaningfulness of slowing the progression of the AD clinical spectrum is recognized as being crucial. Individuals at high risk of or living with dementia, along with their care partners, consistently express the concept of meaningfulness in terms of time across all stages of dementia.[31,32] Significant research has focused on identifying which symptoms, domains, or factors should be measured to capture this meaningfulness.[31,32,48,49] For PLWAD, meaningful time is often defined as the period they can preserve positive aspects of their lives or delay negative experiences. According to Mank et al., 2021, focus group participants frequently posed questions such as, "How quickly will my memory deteriorate?" "When will I no longer feel like myself?" and "When might the end come?".[32] When asked about their ideal treatment, individuals in the early stages of AD often express a desire for a treatment that would allow them to return to their previous state of well-being, or at least halt the progression of their cognitive or functional decline, and to

TABLE 4 Hypothetical treatment effects at 18 months assuming time-saving of 5%, 20%, 30%, 60%, and 95% based on placebo-arm trajectories of seven published anti-amyloid monoclonal antibody clinical trials and ADNI hypothetical placebo arm

		% Slowing over 18 months				
		CDR-SB point differences vs. placebo				
Trial	Baseline CDR-SB (placebo)	5% (~1 month)	20% (~3.5 months)	30% (~5.5 months)	60% (~11 months)	95% (~17 months)
EMERGE	2.49	−0.10	−0.39	−0.56	−1.01	−1.64
ENGAGE	2.40	−0.11	−0.42	−0.60	−0.95	−1.47
CLARITY AD	3.20	−0.07	−0.27	−0.44	−0.96	−1.54
TRAILBLAZER-AZ 2 ALL	3.90	−0.13	−0.49	−0.70	−1.41	−2.26
TRAILBLAZER-AZ 2 LOW/MEDIUM TAU	3.70	−0.12	−0.41	−0.52	−1.07	−1.80
GRADUATE I	3.70	−0.14	−0.55	−0.80	−1.47	−2.19
GRADUATE II	3.50	−0.12	−0.45	−0.64	−1.08	−1.79
ADNI	3.10	−0.08	−0.32	−0.48	−0.98	−1.46

Notes: Data represent the hypothetical differences in CDR-SB change from baseline between active treatment and placebo at 18 months. Light green colors suggest an effect meeting a published MCID for MCI due to AD (0.98), whereas dark green colors suggest an effect meeting a published MCID for mild AD dementia (1.63).
Abbreviations: AD, Alzheimer's disease; CDR-SB, Clinical Dementia Rating scale—Sum of the Boxes; MCI, mild cognitive impairment; MCID, minimal clinically important difference.

retain their current level of abilities. They might say things like, "I want it to make me feel like I did before," "If it could stop now, I could continue to function as I am," or "I could definitely live and manage the way I am now." They also express concerns about the future, stating, "You don't know what's going to happen in the future, how it progresses," and "If it (treatment) can't cure it, just stop the progression—just leave it where it is".[31,50] A systematic review conducted in 2017 identified three studies that provide qualitative evidence or data reflecting that delay in clinical progression is important to persons with MCI or AD dementia, their care partners, and healthcare professionals.[51] In summary, the findings of these studies indicate that delaying or slowing the clinical progression of AD is perceived as profoundly meaningful by PLWAD as well as their care partners to better understand the impact of the treatment. These studies also support the notion that time is a crucial measure of meaningful treatment benefits for those living with or at high risk of developing dementia. However, the amount of time that is required for a delay or the amount of time saved to be considered meaningful will likely vary. We also need to consider the quality of the time saved, not just the amount of time, and when in the course of the condition; addressing this is an even more complex, nuanced, and individualized endeavor. Moreover, evidence from discrete choice experiments involving several hundred care partners of PLWAD and US neurologists support that these stakeholders value and would accept therapy with an amyloid plaque-lowering treatment (including risk of amyloid-related imaging abnormalities [ARIA]) for a longer period of 6 years in order to gain 1 year of delay in clinical progression from mild to the moderate dementia stage of AD.[52]

Published within patients MCIDs on CDR-SB were derived for outcomes measured at approximately 12 months.[25,26] However, when referred to by decision-makers, this time horizon seems to have been neglected.[47]

Our findings showed, that extending the "measurement" time horizon to 24 months increases the point differences on CDR-SB (Figure 1B), in some scenarios beyond the suggested MCIDs. Indeed, the difference in CDR-SB assuming a 30% slowing was estimated at 1.07 points at 24 months versus 0.48 at 18 months; a quite large difference between the two time-points which is explained by the non-linear progression seen in Figure 1B. According to our model-derived estimates from the ADNI cohort simulating a clinical trial of 24 months, a treatment effect of ~25% or ~5.5 months would be required to reach the published MCID for MCI due to AD, and a treatment effect of ~55% or ~13 months would be required for mild AD dementia. This dependence on the time horizon is of course expected for a progressive chronic disease like AD because a slowing of continuously deteriorating symptoms will result in accumulating differences over time.

For additional context, we explored the proportion of participants experiencing substantial decline (defined as 1 point on CDR-SB for MCI and 2 points for mild AD dementia) over 18 months in our ADNI cohort. We found that 48% of participants with MCI and 41% with mild AD dementia experienced such a substantial decline over 18 months. This may be compared to findings from TRAILBLAZER-ALZ 2 in which substantial decline was observed over 18 months in 23% and 37% of donanemab-treated and placebo-treated participants respectively in the low/medium-tau population, and 28% and 41% in the combined population.[11]

More purposefully suited MCIDs for DMTs would be helpful when evaluating evidence from clinical trials. A suggestion for sponsors to simply increase sample sizes of trials to increase the chances of detecting statistical significance for "small" effects on clinical outcomes fails to acknowledge that the meaningfulness of a disease-slowing treatment needs to be assessed relative to the untreated progression for

the population over the corresponding time period.[22] Better derived and appropriately applied MCIDs might indeed help decision-makers better judge the relevance of a treatment effect. However, one cannot simply disregard that the purpose of disease modification is to gain accumulating benefits over a longer time horizon than the duration of a feasible randomized, blinded, and placebo-controlled clinical trial. It is likely that a slowing over 18 months would postpone milestones of disease that have not yet occurred at the end of the 18-month period, even if treatment is stopped at 18 months. This long-term benefit, along with a potentially increasing delay with continued treatment, should be taken into consideration when evaluating the value of a specific disease delay. Arguably, it is plausible that PLWADs would weigh in on their long-term expectations when judging whether the time saved is meaningful or not. These data are greatly needed and must emerge to better inform the field, and its multiple stakeholders, and to help benefit PLWAD and their families.

5 | CONCLUSION

Our findings show that, if MCIDs based on within-patient point savings on the CDR-SB are applied to between-group differences for treatments that slow disease progression, only those saving nearly one year with 18 months of treatment in MCI would be considered meaningful, and for mild dementia, even a complete halting of the disease would not be considered clinically meaningful. This suggests that decision-makers should not be influenced by published MCIDs, as this may be misguided, and to the detriment of patients, families, and a broader AD community.

In conclusion, published MCIDs in AD are incompatible with the expected benefits of disease modification. Even inarguably meaningful slowing of AD clinical progression would at best result in short-term clinical trial effect sizes which with currently applied MCID cut-offs would result in conclusions that are not face valid and would erroneously consider many months of time saved as either non- or only borderline-meaningful. Translating trial endpoints to estimates of time saved shows that often referenced suggested MCIDs are not relevant, and contradict known realities, failing to align with PLWAD person-centered approaches. There is a pressing need to develop more purposeful MCIDs using PLWAD person-centered approaches, that is, MCIDs that are guided by the experiences and preferences of PLWAD and their care partners.

5.1 | Limitations

This study has limitations. First, our study estimates the time saved in AD progression over an 18-month and 24-month period only, while the time saved concept is likely implicitly perceived as being persistent beyond this time frame. Because AD is a progressive disease, any considerations of meaningfulness are likely to depend on the time horizon considered. Second, and similar to the previous point, meaningfulness is also likely dependent on the stage of disease. Indeed, we compared our findings to suggested MCIDs for different stages, but our analysis of the ADNI data did not allow for separate estimates by severity or stage of disease. Third, the estimates of AD clinical progression slowing presented in our analysis are contingent upon the choice of outcome measures, such as the CDR-SB, their consideration of the multifactorial symptoms of AD, and the precision and timing of the measurements. Alternative more sensitive outcome measures, or measures of specific cognitive, behavioral, and functional domains, could potentially yield different estimates of clinical progression. Fourth, our findings show that AD clinical progression in the ADNI cohort was slower compared to historical placebo arms of clinical trials. This difference underscores the variability in disease progression rates between observational studies and controlled clinical trial settings, and between studies with different inclusion/exclusion criteria and populations, methodology, and precision and timing of outcome measurements.

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CONFLICT OF INTEREST STATEMENT

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Exciva, Ironshore Pharmaceuticals, H Lundbeck A/S, Novo Nordisk, Otsuka, and Praxis Therapeutics. Anders Gustavsson is a partner of Quantify Research, providing consultancy services to pharmaceutical companies and other private and public organizations and institutions. He indirectly owns shares in and serves on the board of Mindmore AB. Soeren Mattke serves on the board of directors of Senscio Systems, Inc., and the scientific advisory board of AiCure Technologies, Alzpath, and Boston Millennia Partners. He has received consulting fees from Biogen, C2N, Eisai, Novartis, and Roche/Genentech. Linus Jönsson has received research funding for his institution from VINNOVA, FORTE, IHI, Novo Nordisk, serves on an advisory board for Servier, and receives license fees for the RUD instrument. Thomas Maltesen is an employee of Novo Nordisk. He owns shares in Structure Therapeutics Inc. ADR, NNIT A/S, and EVOTEC AG. Pepa Polavieja is an employee of Novo Nordisk and is a minor shareholder in Eli Lilly. Teresa León is an employee of Novo Nordisk and is a minor shareholder in Novo Nordisk and PharmaMar. She has received consulting fees from Lexeo Pharmaceuticals, Healios and Mynorix (2021–2022). Julie Hviid Hahn-Pedersen is an employee of Novo Nordisk and is shareholder in Novo Nordisk. Author disclosures are available in the Supporting Information.

CONSENT STATEMENT

All appropriate author consent has been obtained. Other consent is 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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