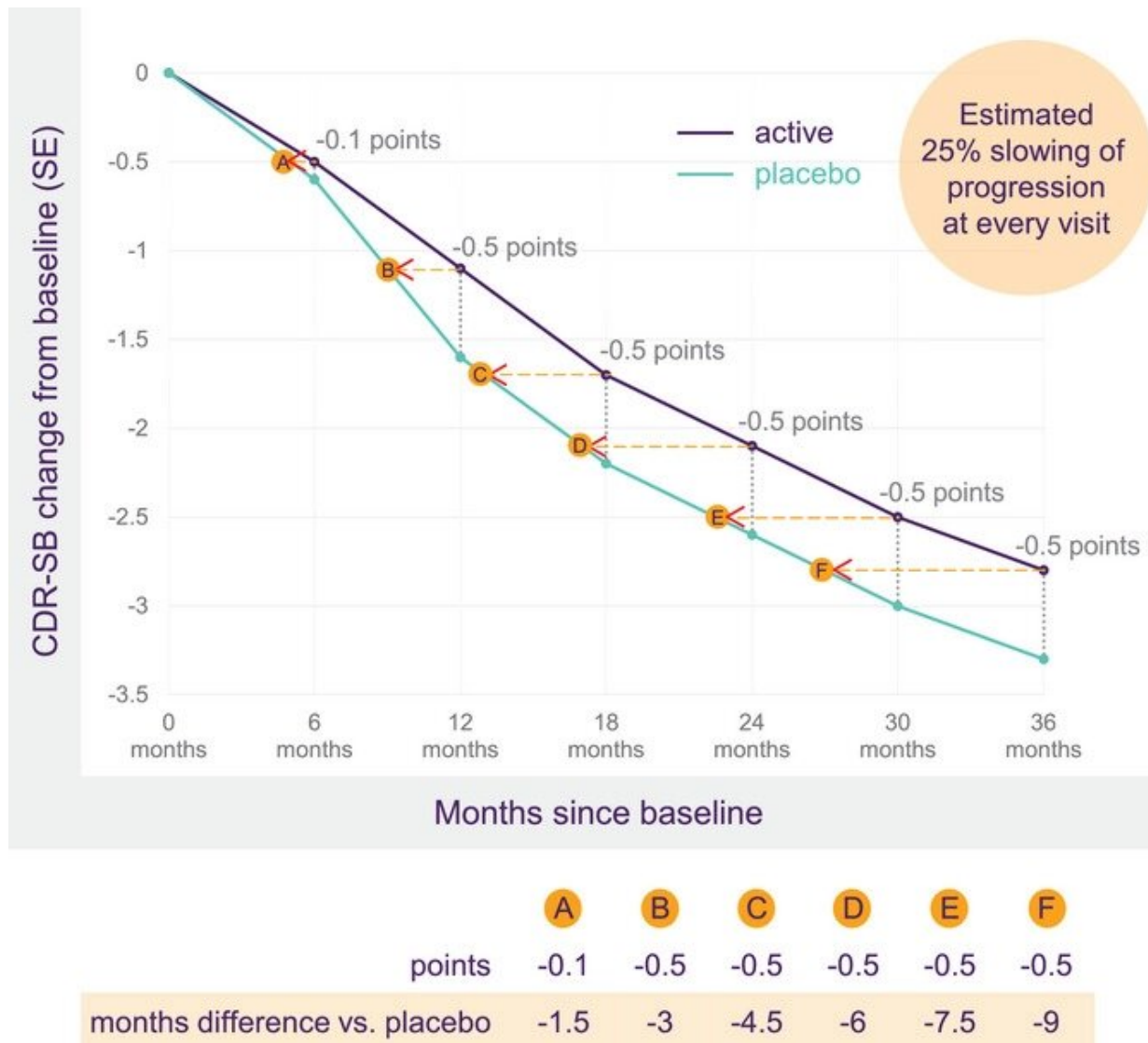


Experts reframe 'clinical meaningfulness' in Alzheimer's

February 7 2023



A progression model for repeated measures (PMRM), adapted from Raket, illustrates the time savings between a CDR-SB change score at a specific time

point and the slowing or delay of disease progression. Credit: *Alzheimer's & Dementia* (2023). DOI: 10.1002/alz.12959

As the Alzheimer's disease scientific community, patients, and families seek to understand the results of clinical trials of new Alzheimer's treatments, the Alzheimer's Association convened an expert work group to discuss an important and timely issue: the "clinical meaningfulness" of results from these studies. Their findings and recommendations are published online today by *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*.

A 2021 article from the Alzheimer's Association Research Roundtable referenced the U.S. Food and Drug Administration (FDA) description of clinical meaningfulness as when "the [treatment](#) has a positive and significant effect on how an individual feels, functions, or survives."

Interpretations of clinical meaningfulness are used by agencies, such as the FDA, and public and private payers, such as Medicare, in their decision making about approval and coverage of treatments. It thus becomes an important topic for researchers and clinicians in their efforts to develop and prescribe treatments, and fuels discussions of the benefits and risks of new drugs.

In January 2022, the Alzheimer's Association asked a work group of experienced and internationally-recognized clinicians and researchers to examine and redefine—with patients' and families' needs at the forefront—what is considered a meaningful benefit or slowing of Alzheimer's. They found that:

- Simply slowing the progression of the disease—rather than halting it, which may come eventually—has measurable and

meaningful benefits for patients and their families, especially in early Alzheimer's when cognition and memory are mostly intact.

- A statistically significant benefit in an 18-month clinical trial may signify and lead to an even more meaningful change when projected out over succeeding years.
- It is unlikely that any single intervention on dementia-related brain changes will have a large clinical effect on its own. For greater impact, combination therapies will be needed, just as we treat elevated blood pressure and cancer today.

According to the work group, if treatments are continued long-term—longer than the 18 months of a typical Phase 3 Alzheimer's trial—and sustain their effectiveness at the same "modest" levels as in the clinical trial, they would be expected to show cumulative benefits that become bigger, more readily apparent and more meaningful over time. The authors suggest we may need to modify our expectations of treatment outcomes in relatively brief Alzheimer's clinical trials.

"This is a trailblazing era of Alzheimer's treatment that calls for mold-breaking thinking," said Ronald C. Petersen, M.D., Ph.D., director of the Mayo Clinic Alzheimer's Disease Research Center and the Mayo Clinic Study of Aging, and lead author of the journal article. "Early intervention over an 18-month Alzheimer's clinical trial has been shown to slow disease progression and provide noticeable and measurable benefits to patients and their families."

"A 20-30% slowing of disease progression initiated in the earlier stages of Alzheimer's could mean more time in the less impaired and more functional stages of the disease, as well as delay the onset of severe decline," Petersen added. "The newly-approved Alzheimer's drugs are not the ultimate answer but they are an important first step in the right direction."

Petersen further suggests that preserving function, even for four to six months over a timeframe of 18 months, can be essential for maintaining independence and autonomy, which is the crux of meaningfulness for people with early Alzheimer's. For example, with respect to driving, in some states, persons diagnosed with dementia may need to be reported to the department of motor vehicles, while those with [mild cognitive impairment](#) may continue to drive with appropriate observation. That preservation of function can be very meaningful.

For treatments that slow Alzheimer's disease progression, the situation is complex because two variables must be considered. One is the change in the treatment group relative to placebo on tests of memory, thinking and daily function, and the other is time. In other words, when and how long did it take for that difference in cognitive score to be achieved?

"Will long-term cognitive benefits be greater than what we saw at 18 months? We believe they will be," said Maria C. Carrillo, Ph.D., Alzheimer's Association chief science officer and senior author of the newly-published article. "The work group expressed that the benefits of these therapies are likely to increase beyond the 18-month period observed in clinical trials. But it is important that clinicians discuss the changing risk/benefit ratio with their patients and families."

The Alzheimer's Association recently launched ALZ-NET, a provider-enrolled network that collects long-term clinical, imaging and safety data from patients treated with FDA-approved Alzheimer's disease therapies in real world clinical settings.

The work group suggests, "It is unlikely that any single intervention on dementia-related brain changes—amyloid, tau, vascular [disease](#), alpha-synuclein or TDP-43—is likely to have a large clinical effect on its own. Nevertheless, halting one aspect ... may likely produce a modest benefit, but a real one." They argue that combination therapies will be a necessity

moving forward for even more meaningful benefit.

As an illustration, the authors say, "Just as we treat hypertension today with diuretics, beta-blockers, calcium channel antagonists, angiotensin-receptor blockers, angiotensin converting enzyme inhibitors and the like to treat one symptom (elevated [blood pressure](#)) we will likely need multiple therapeutic interventions to address complex pathological and cognitive issues of aging. Combination therapy in oncology has also been a very successful approach for cancer treatment."

More information: Ronald C. Petersen et al, Expectations and clinical meaningfulness of randomized controlled trials, *Alzheimer's & Dementia* (2023). [DOI: 10.1002/alz.12959](https://doi.org/10.1002/alz.12959)

ALZ-NET: www.alz-net.org/

Provided by Alzheimer's Association

Citation: Experts reframe 'clinical meaningfulness' in Alzheimer's (2023, February 7) retrieved 26 April 2024 from <https://medicalxpress.com/news/2023-02-experts-reframe-clinical-meaningfulness-alzheimer.html>

<p>This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.</p>
--